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EARLY DIAGNOSIS OF CANCER BY STUDY OF EXFOLIATED CELLS

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Until the cause or causes of cancer are discovered, the only way cancer can be controlled is by early diagnosis and the consequent eradication of the malignant lesion at its inception. In the majority of cancers early diagnosis is not now possible. How is the physician to suspect, much less perform a biopsy of, a symptomless cancer of the stomach or lung which cannot be visualized? How shall one suspect cancer of the cervix in the presence of a grossly normal organ and before abnormal bleeding? In many parts of the body malignant lesions present for months or even years may be attended by their first clinical symptom only after invasion or metatasis has taken place.

Because of its recognized value and in order to check its misuse we propose to outline the present status of the cytologic method of cancer diagnosis. We believe that in certain regions of the body an earlier diagnosis of cancer can be made through proper use of this method than can be achieved by any other means. Particularly is this true of cancer of the uterus and the lung. There is reason to hope that detection of early cancer of the stomach and the urinary tract may also become practicable by the use of the cytologic technic.

After six years of extensive experience with the study of exfoliated cells at the Massachusetts General Hospital, it is our conviction that the cytologic method has become an essential procedure for the early diagnosis of many types of malignant disease. In its use, however, as in any diagnostic maneuver, judgment must be used, and those making the diagnosis must be completely familiar with the technic. Forty years ago William Osler wrote: "To be exploited prematurely in practice is the common fate of all new scientific facts. Not content to wait for full knowledge, men hastily draw conclusions from imperfect data." Exploitation of the diagnostic method to be discussed has already occurred.[1] Reliance on a diagnosis, for or against cancer, submitted by an inexperienced "cytologist" constitutes malpractice as surely as does the performance of a major operation by an inadequately equipped surgeon. The misuse and exploitation of this method by untrained persons cannot be tolerated.

The story of cytologic diagnosis begins over one hundred years ago when Pouchet[2] first examined unstained preparations of vaginal fluid in an attempt to analyze the normal sexual cycle. Seventy years later, in 1917, Stoeckard and Papanicolaou,[3] seeking a way of studying the consecutive stages of estrus in the guinea pig, reexamined the vaginal secretion. They developed the technic of rapid fixation and staining which made possible for the first time accurate cytologic observation of the vaginal fluid. In the rodent, the study of the vaginal secretion proved unexpectedly rewarding. A specific cytologic picture was seen for each successive phase of the estrous cycle, thus making accurate identification of each phase possible. In human beings, however, results of vaginal smears have proved disappointing. Although a vaginal epithelial rhythm is present in women, the clearcut sequence of cytologic events observed during the estrous cycle in the guinea pig is not observed. Specific changes dependent on ovulation are not seen. In the normal woman, the changes visible in the vaginal secretion following ovulation are due not to the specific action of progesterone but to the decrease in estrogen secretion which follows follicle rupture. Similar changes occur whenever estrogen is suddenly withheld from a previously estrogen-treated castrate female subject. Papanicolaou[4] said, "The vaginal smear offers only indirect evidence as to ovulation and the time of its occurrence." Quantitative changes in the amount of estrogen, however, may be estimated by the vaginal smear, and the test is, therefore, useful in determining the functional activity of the ovaries (or of extraovarian sources of estrogen) and in judging the adequacy of estrogen therapy in postmenopausal women.

In 1923 Papanicolaou became impressed by the abnormal features of certain cells observed in the vaginal secretion of women with cancer of the uterus and suggested that the vaginal smear should be useful in the diagnosis of malignant uterine disease. His first

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1. Scheffey, L. C., and Rakoff, A. E.: The Cytology Test for Uterine Cancer, Philadelphia Med. 43: 435, 1947. The Papanicolaou Test for Uterine Cancer, editorial, J. A. M. A. 136: 331-332 (Jan. 31) 1948.

2. Pouchet, F. A.: Théorie positive de l'ovulation spontanée et de la fécondation des mammifères et de l'espèce humaine, basée sur l'observation de toute la série animale, Paris, J-B. Baillière, 1847.

3. Stockard, C. R., and Papanicolaou, G. N.: The Existence of Typical Oestrous Cycle in Guinea-Pig, with a Study of Its Histological and Physiological Changes, Am. J. Anat. 22: 225-283, 1917.

4. Papanicolaou, G. N.: A General Survey of the Vaginal Smear and Its Use in Research and Diagnosis, Am. J. Obst. & Gynec. 51: 316-328, 1946.

publication[5] on this subject appeared in 1928 and a second[6] in 1933. Little interest, however, was aroused by his early observations. Six years devoted to a study of other aspects of vaginal cytology passed before Papanicolaou again[7] in 1941 reiterated his conviction that uterine cancer could be accurately diagnosed by vaginal smear. This publication focused our attention on the problem and we[8] were the first to confirm Papanicolaou's results. Evaluation of the method is still in progress and its applicability to the diagnosis of cancer in other organs besides the uterus is under active investigation.

The biopsy remains the final method of establishing a diagnosis of cancer; until recent years it has been the only means by which a diagnosis of cancer could be made. Any alternative method to be acceptable must be theoretically sound, statistically reliable and superior, at least in certain respects, to biopsy. Evidence will be presented that the cytologic method fulfils these requirements.

RATIONALE

Diagnosis by the cytologic method depends on the fact that malignant tumors on any free surface desquamate tumor cells into the surrounding medium. It is known that there exists a continuous exfoliation of cells from every epithelial surface of the body. Thus the vaginal secretion, the sputum and the urine normally contain cells desquamated from the corresponding epithelial surfaces. There is evidence[9] that tumor cells may desquamate even more rapidly than normal cells and that such malignant cells can be accurately identified. If the presence of tumor cells in any body fluid is correctly established, such cells must have taken origin from an area of tumor proximate to or in contact with the fluid examined.

Criteria have been established[10] for the identification of malignant cells and their differentiation from the many types of normal cells exfoliated into the body fluids. These criteria are based on recognizable morphologic changes in the nucleus and cytoplasm of cells found in the body fluids of patients with malignant disease, and not found in the absence of malignant lesions. Direct smears from malignant tumors obtained at operation show cells identical with those present in the body fluid of the person bearing the tumor.[8a]

That fundamental alterations in structure accompany the transition of normal into malignant cells is suggested by observations of Firor and Gey.[11] These investigators studied in vitro cultures of normal rats' fibroblasts. On three occasions some of the normal fibroblasts became permanently altered; inoculation of young healthy rats with the altered cells was followed by the development of sarcomas at the point of inoculation.

The authors said:

> At first the newly altered cells showed nuclei that were slightly larger than those of the cells of origin. Later the nuclei became irregular in outline, very granular, and in stained preparations, the altered nuclei were hyperchromatic. . . . The changes just described were shown to be coincident with the development of malignant characteristics, for when colonies of altered and unaltered cells were inoculated into the rats, the former produced sarcoma at the sites of inoculations, the latter never did.

It is significant that the cellular changes accompanying malignant transformation in rats' fibroblasts, namely, enlargement of the nucleus, enlargement of nuclear granules and nuclear hyperchromatism in stained specimens, are identical with the morphologic alterations commonly observed in cells desquamated from human cancer. The differentiation of cancer cells from normal cells in body fluids depends to a large degree on these very criteria.

COLLECTION OF MATERIAL

The collection of material for examination is simple. In the case of vaginal smears, a pipet 6 inches (15 cm.) long with capillary opening and capped by a rubber suction bulb is introduced into the posterior vaginal fornix; the bulb is released and aspirated fluid is blown on a previously marked glass slide, which is immediately dropped into a fixative of equal parts of 95 per cent alcohol and ether. Neither douching nor pelvic examination should precede the collection of the specimen.

Sputum is spread thinly on glass slides and similarly fixed. Search is made to obtain blood-flecked bits of sputum for examination.

For examination of the urine an entire fresh morning specimen is centrifuged and the sediment spread on three slides which have been previously covered with egg albumin. The slides are fixed in alcohol and ether. Ten cubic centimeters of 40 per cent formaldehyde may be added to the urine if immediate centrifuging is not possible.

For the cytologic study of gastric contents our laboratory now examines two specimens. The first is the fasting gastric content, secured through a Levin tube with additional openings cut in its terminal 8 inches (20 cm.). The tube is passed in the usual manner and the patient allowed to drink water during its passage. After the stomach is emptied, 100 cc. of isotonic solution of sodium chloride is injected and allowed to come in contact with all surfaces of the organ by turning the patient on either side and face downward and by having him walk about. The fluid is forcibly aspirated and reinjected several times during this period. Both specimens are centrifuged and the sediment smeared thinly on glass slides and fixed and stained in the usual way.

All preparations are stained by Papanicolaou's method, details of which may be found in previous publications.[12]

While the technic of preparation is simple, the ability to make accurate diagnoses by this method is difficult to acquire, obtainable only by months of intensive training and perfected only through constant use. A physician or laboratory technician examining a few preparations a month cannot obtain competence in this diagnostic technic. The differentiation of cancer cells from normal cells, be they in tissue preparations or smears, belongs within the province of the pathologist. If diagnosis by exfoliative cytology is as valuable as many of us believe, it must become the responsibility of the pathologist to acquire the same skill in the interpretation of smears that he now possesses in the diagnosis of tissue sections.

5. Papanicolau, G. N.: New Cancer Diagnosis, Proceedings of Race Betterment Conference, 1928, pp. 528-534.

6. Papanicolaou, G. N.: The Sexual Cycle in the Human Female as Revealed by Vaginal Smears, Am. J. Anat. (supp.) 52: 519-637, 1933.

7. Papanicolaou, G. N., and Traut, H. F.: The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus, Am. J. Obst. & Gynec. 42: 193-206, 1941.

8. (a) Meigs, J. V.; Graham, R. M.; Fremont-Smith, M.; Kapnick, I., and Rawson, R. W.: The Value of the Vaginal Smear in the Diagnosis of Uterine Cancer, Surg., Gynec. & Obst. 77: 449-461, 1943. (b) Meigs, J. V.; Graham, R. M.; Fremont-Smith, M.; Jansen, L. T., and Nelson, C. B.: The Value of the Vaginal Smear in the Diagnosis of Uterine Cancer, Surg., Gynec. & Obst. 82: 337-345, 1945.

9. Coman, D. R.: Decreased Mutual Adhesiveness, a Property of Cells from Squamous Cell Carcinomas, Cancer Research 4: 625-629, 1944.

10. Papanicolaou, G. N., and Traut, H. F.: Diagnosis of Uterine Cancer by the Vaginal Smear, New York, The Commonwealth Fund, 1943; footnote 7.

11. Firor, W. M., and Gey, G. O.: Observations on the Conversion of Normal into Malignant Cells, Ann. Surg. 121: 700-702, 1945.

12. Papanicolaou and Traut.[10] Papanicolaou, G. N.: A New Procedure for Staining Vaginal Smears, Science 95: 438-439, 1942.

CANCER OF THE UTERUS

Of the two types of uterine cancer, carcinoma of the cervix presents by far the more serious problem. Found in women in their forties and early fifties, five times as often as is endometrial cancer, cervical carcinoma develops more insidiously and metastasizes earlier. Its occurrence, moreover, proves a calamity not only for the patient but for her entire family, as the majority of the victims are women in the prime of life, often the mothers of young children.

Although the cervix is readily visualized and cancer of this organ is believed to give early evidence of its presence either by abnormal bleeding or by the development of a visible lesion, cervical cancer is often still diagnosed only in an advanced stage. Recently it has been recognized that cancer of the cervix may exist for months or years before the appearance of either symptom or sign. The average age at which evidence of cervical cancer appears is known to be 48 years. TeLinde and Galvin [13] and Pund and Auerbach [14] found 36 years to be the average age for the appearance of carcinoma *in situ*. Younge [15] found carcinoma *in situ* in 135 women, whose average age was 38 years. Thus cancer of the cervix must occur on the average ten years before clinical evidence of its presence.

When abnormal bleeding does appear usually in the late forties, such bleeding is too commonly ascribed by both patient and physician to menopausal irregularity, and examination, therefore, is postponed. At the time bleeding first appears, however, the situation is often already grave. Maliphant,[15a] studying 837 cases of cervical cancer, observed the disease to be in an advanced stage in 60 per cent of women seen six months after the onset of spotting and advanced disease in 50 per cent of those examined only three months after the onset of spotting. Todd [16] has estimated that from onset of bleeding chances of cure decrease 3 per cent per week. The average delay from the onset of abnormal bleeding to the institution of treatment is seven and a half months.[17] Thus lives are lost because the diagnosis of cancer may not even be suspected until the disease is beyond hope of cure. While routine biopsy, if correctly performed, will reveal most cases of early cancer, biopsy is a hospital procedure except in the office of the gynecologic specialist. It is, moreover, manifestly impracticable to obtain repeated biopsy specimens from symptomless women. The vaginal smear, on the other hand, is technically simple to procure. If sufficiently accurate, the vaginal smear should offer a means of detecting cervical cancer earlier than can be practically accomplished in any other way.

In 1947 statistics concerning approximately 5,000 patients examined by vaginal smear were collected by Gates and Warren.[18] Estimates of accuracy of the vaginal smear varied from 96 to 99 per cent. However, the authors correctly remarked that by the inclusion in any series of an increasing preponderance of negative results, the apparent accuracy of the test can be made to approach 100 per cent.

Since Gates' and Warren's compilation, Isbell, Jewett, Allan and Hertig [19] have reported 1,045 cases, including 58 proved cases of cancer of the uterus, in which again the over-all accuracy of the vaginal smear was 98.5 per cent. Of 40 cases of carcinoma of the cervix, positive smears were obtained in 39. Of 18 cases of malignant disease of the fundus, however, smears were positive in 15, and negative in 3.

Scheffey, Rakoff and Hoffman [20] reported, in 1948, 63 proved cases of cancer in 500 consecutive gynecologic admissions. The over-all accuracy of the vaginal smear method was 95 per cent. However, positive smears were obtained in only 70 per cent of cervical and 67 per cent of endometrial cancers.

Our experience in the Vincent Memorial Laboratory in the years 1942 to 1947 is based on the examination of vaginal smears from 5,621 women, of whom 492 had uterine cancer. All figures are based on the initial smear report. This series includes 113 cases of endometrial carcinoma, in 83 of which diagnosis was made by smear, an error of 26.5 per cent; and 354 cases of cervical carcinoma, in 317 of which diagnosis was made by smear, an error of 10.5 per cent. There have been 69 cases in which a positive diagnosis made by smear was not confirmed at pathologic examination. This represents a "false positive" diagnostic error of 1.3 per cent. It is evident that if cases with proved cancer only are considered, the smear fails to detect the malignant disease in about 20 per cent of endometrial and 10 per cent of cervical carcinoma. As will later be seen, biopsy likewise misses some 10 per cent of cervical cancers.

Of particular interest is a group of preinvasive carcinomas of the cervix studied at the Vincent Memorial Laboratory both by vaginal smear and by biopsy. Sixteen cases have already been reported.[21] The number has now been increased to a total of 30 cases.

Thirteen of these 30 women (or nearly 50 per cent) presented no gynecologic symptoms. The initial vaginal smear was positive in 23. Biopsies were performed for 27 of the same patients. The results of the initial biopsy were positive in 13, questionable in 4 and negative in 8. In 2 cases no tissue was obtained. In 2 cases in which cancer was missed by vaginal smear, the result of the initial biopsy was correctly positive. Thus in a series of 30 cases, the initial vaginal smear proved significantly more accurate than did the initial biopsy in detecting preinvasive cancer of the cervix.

A comparison of the accuracy of the vaginal smear with that of the biopsy in 181 cases of proved epidermoid carcinoma of the cervix was made by Graham, Sturgis and McGraw.[22] In this series the result of

13. TeLinde, R. W., and Galvin, G.: The Minimal Histological Changes in Biopsies to Justify a Diagnosis of Cervical Cancer, Am. J. Obst. & Gynec. 48: 774-797, 1944.

14. Pund, E. R., and Auerbach, S. H.: Preinvasive Carcinoma of the Cervix Uteri, J. A. M. A. 131: 960-963 (July 20) 1946.

15. Younge, P.: Study of One Hundred and Thirty-Five Cases of Carcinoma-in-Situ at the Free Hospital for Women, personal communication to the authors.

15a. Maliphant, R. G.: Cancer of the Cervix Uteri: The Results of Treatment with Radium, J. Obst. & Gynaec. Brit. Emp. 54: 155-163, 1947.

16. Todd, O. E.: Cancer of the Cervix: Time Wasted, J. Michigan M. Soc. 40: 191-196, 1941.

17. Todd.[16] Hodge, R. H.: Carcinoma of the Cervix: Time Lost Before Treatment, Virginia M. Monthly 69: 200-203, 1942. Leach, G. E. and Robbins, G. F.: Delay in the Diagnosis of Cancer, J. A. M. A. 135: 3-8 (Sept. 6) 1947.

18. Gates, O., and Warren, S.: A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears, Cambridge, Mass., Harvard University Press, 1947, p. 5.

19. Isbell, N. P.; Jewett, J. F.; Allan, M. S., and Hertig, A. T.: A Correlation Between Vaginal Smear and Tissue Diagnosis in 1,045 Operated Gynecologic Cases, Am. J. Obst. & Gynec. 54: 576-583, 1947.

20. Scheffey, L. C.; Rakoff, A. E., and Hoffman, J.: An Evaluation of the Vaginal Smear Method for the Diagnosis of Uterine Cancer, Am. J. Obst. & Gynec. 55: 453-460, 1948.

21. Fremont-Smith, M.; Graham, R. M., and Meigs, J. V.: Vaginal Smears as an Aid in the Diagnosis of Early Carcinoma of the Cervix, New England J. Med. 237: 302-304, 1947.

22. Graham, R. M.; Sturgis, S. H., and McGraw, J. A.: A Comparison of the Accuracy in Diagnosis of the Vaginal Smear and Biopsy in Carcinoma of the Cervix, to be published.

the initial biopsy was correctly positive in 90 per cent; the initial vaginal smear was correct in 91 per cent. The two methods combined achieved a diagnostic accuracy of 99 per cent. In this connection it seems appropriate to quote the words of two conservative investigators. Isbell and Hertig said: "The [vaginal smear] method has proved unexpectedly valuable in the study of early carcinoma and carcinoma-in-situ as well as in the diagnosis of more advanced cases." Gates and Warren commented: "Overemphasis on the statistical accuracy seems to put the stress in the wrong place . . . the thing that matters is whether the use of the method will discover cancer and initiate treatment earlier than would otherwise be done."

Annual deaths in the United States from carcinoma of the cervix approach 17,000. All, or a great majority, of these women could be saved were the cancer discovered sufficiently early. In how many women will early cancer of the cervix be found? Estimates of the incidence of carcinoma *in situ* of the cervix vary from 0.29 per cent (Gates and Warren [18]) to 3.7 per cent (Pund and Auerbach [14]). Younge [15] examined 955 routine cervical biopsy specimens taken in the Outpatient Department of the Free Hospital for Women and found 11 instances of carcinoma *in situ* (1.15 per cent).

The majority of women with preinvasive cancer have no symptoms, and the cervix gives little indication of disease. Of Pund's and Auerbach's 47 patients, only 1 out of 4 had abnormal bleeding, and the presence of cancer was not recognized from the gross appearance of the cervix in a single case. Of Younge's 135 patients, 46 per cent were symptomless, 80 per cent showed what was described as an "innocent erosion" of the cervix, 7 per cent presented frankly normal cervices and in only 6 per cent was the cervix considered "suspicious." In 2 of Younge's patients, each with a diagnosis from biopsy of carcinoma *in situ*, invasive carcinoma developed after intervals of three and a half years and one year, respectively. The way to prevent the development of uncontrollable advanced cervical cancer is by discovery and eradication of the early lesion before invasion or metastasis has occurred. It is evident that detection of early unsuspected cervical cancer should be possible by vaginal smear.

Few reports of screening by vaginal smear have appeared. Pund and his collaborators [23] detected 7 cases of preinvasive carcinoma by routine endocervical smears. The total number of women examined was not given. Kraushaar [24] took a single vaginal smear from all women over the age of 30 admitted to the Hospital of the University of Iowa since January 1947; 1,931 women were so examined. Sixty-two positive smears were obtained, 52 of which were confirmed by tissue pathologic examination and 2 by clinical examination. Negative results of biopsies were obtained in 3 cases with positive smears. In 12 cases the smear failed to disclose uterine carcinoma later discovered in tissue section. In reference to a larger series, of about 4,000 cases, Kraushaar wrote: "We have detected by smears and proven by tissue sections 12 cases of carcinoma of the cervix, either as carcinoma-in-situ or early epidermoid carcinoma, in which the cervix appeared to be normal clinically." Palermo,[25] screening 827 gynecologic patients, discovered three unsuspected cervical carcinomas. Scheffey and Rakoff [20] found only 7 cases of uterine carcinoma in a screening of approximately 5,000 cases, including many young women.

We [26] have published the results of screening 200 unselected office patients by vaginal smear. The series now totals 358 women, each examined by a single vaginal smear. These women came to the office of an internist for general physical examination. Only 25 complained of either bleeding or abnormal discharge. Six positive smears were obtained, 5 of which were confirmed by pathologic examination—carcinoma *in situ* of the cervix in 4 and endometrial cancer in 1 case. Of the 4 patients with cervical cancer, no gynecologic symptoms were present in 2 and the cervix was normal to visualization in all. This small series tends to confirm previous evidence that about 1 woman in every hundred bears in her cervix an early malignant lesion, often invisible and symptomless. The discovery of even one preinvasive cancer justifies the examination of many smears. Whether screening by smear as a public health measure will become economically practicable is a question that cannot now be answered.

M. B., a woman of 43, came to my office complaining of diarrhea and arthritis. There had been no bleeding or discharge. Routine examination disclosed a lacerated cervix. Vaginal smears were twice positive for cancer. A biopsy showed carcinoma *in situ*. A Wertheim hysterectomy was performed by Dr. Meigs. According to the pathologic report the cervix appeared normal grossly. Microscopic examination disclosed squamous cell carcinoma *in situ*.

D. C., age 42, complained of a mass in the breast. There was no vaginal bleeding or discharge. The cervix appeared normal. A vaginal smear was doubtful and a repeat smear positive. Results of biopsy were positive for cancer. A total hysterectomy was performed. No gross lesion was visible, but microscopic examination showed squamous cell carcinoma *in situ*.

A. S. had no symptoms. A routine vaginal smear was positive. A week later a second smear was positive and biopsy revealed epidermoid carcinoma *in situ*. A total hysterectomy was performed by Dr. Meigs. Pathologic examination revealed epidermoid carcinoma *in situ*.

Without a routine vaginal smear these and similar cases of early cervical cancer would not have been discovered. How many women in their early forties with neither bleeding nor discharge and with a cervix normal to inspection would be sent to a gynecologist for biopsy, and with what likelihood that a biopsy specimen, if taken, would contain the area bearing the cancer?

At this point a word should be said as to the significance of vaginal smear reports. A negative smear does not exclude the possibility of cancer. As has been stated, the initial smear will miss about 1 case of cervical carcinoma in 10. A report of positive results indicates biopsy or curettage; it does not indicate operation. An occasional false positive result is inevitable. Biopsy confirmation must be obtained in every case before operation is advised.

23. Pund, E. R.; Neiburgs, H. E.; Nettles, J. B., and Caldwell, J. D.: Preinvasive Carcinoma of the Cervix Uteri: Seven Cases in Which It Was Detected by Examination of Routine Endocervical Smears, Arch. Path. 44:571-577 (Dec.) 1947.

24. Kraushaar, O. F.: Personal communication to the authors.

25. Palermo, A. A.: Personal communication to the authors.

26. Fremont-Smith, M., and Graham, R. M.: The Vaginal Smear: Its Value to the Internist, with Report of Diagnosis of Unsuspected Uterine Cancer in Four Cases, J. A. M. A., 137:921-922 (July 10) 1948.

CARCINOMA OF THE LUNG

In carcinoma of the bronchus, early diagnosis is rarely made. Early in the disease a definitive diagnosis by roentgenogram or bronchoscope is usually impossible. Herbut and Clerf [27] stated that by the time cancer is positively diagnosed by bronchoscopic examination or by biopsy, ". . . the lesion has too often infiltrated such vital structures that surgical extirpation is impossible."

Attempts to diagnose bronchogenic carcinoma by examination of sputum or bronchial secretion have been increasingly successful.

Dudgeon [28] (1937) found evidences of carcinoma from the examination of sputum smears in 77 per cent of 56 cases. Gowar [29] (1943) reported the observation of tumor cells in 64 per cent of 93 cases. Wandall [30] (1944) diagnosed the disease correctly by sputum examination in 84 per cent of 100 cases of bronchogenic carcinoma.

Herbut and Clerf [31] reported the detection of cancer cells in the bronchial secretion of 25 (92.5 per cent) of 27 consecutive cases with carcinoma of the bronchus; the disease in 12 cases with completely negative results of bronchoscopic examination was correctly diagnosed by smear. These authors stated that by cytologic study the disease in an additional 20 to 25 per cent of cases, with lesions beyond bronchoscopic vision can be diagnosed; and stressed that this percentage represents those cases in which the growth is most amenable to complete surgical removal. To date a total of 800 patients, including 180 with proved bronchial carcinoma, have been examined by Herbut.[32] Cancer cells were observed in bronchial secretion of 161, or 89 per cent. By contrast the results of biopsy were positive in only 71 cases, or 39 per cent. Results of examination of secretions were positive and results of bronchoscopy completely negative in 51, or 29 per cent.

McKay and his co-workers [33] studied smears of secretion obtained in 170 bronchoscopic examinations. Of the 54 cases in which bronchogenic carcinomas were encountered, tumor cells were observed in 40 (74 per cent). Three false positive diagnoses were made. In 14 cases of bronchogenic carcinoma (25 per cent), results of bronchoscopy were negative and the smear was positive. Two further cases were reported with peripheral tumors not visualized at bronchoscopy. In both cases the smear was positive for tumor cells. Woolner,[34] examining bronchial secretion or sputum from 2,200 patients, obtained 200 positive smears. Only 4 of the 200 smears were proved to be false positive. Negative smears were obtained in about 10 per cent of cases of bronchial carcinoma.[35]

Diagnoses based on examination of sputum are still regarded with skepticism by the clinical services, although in the Vincent Memorial Laboratory during the past year, not one false positive diagnosis based on examination of sputum has been made.

A 44 year old man complaining of cough of ten days' duration had dulness and bronchial breath sounds over the upper lobe of the right lung. Roentgenograms were suggestive of tuberculosis. Results of three sputum examinations were positive for cancer. On rounds "no one was convinced of the likelihood of tumor." At autopsy carcinoma of the bronchus and abscess of the upper lobe of the right lung were present.

A. G., a man of 63, complained of cough for a period of seven months. The diagnosis based on roentgenologic observations was pulmonary abscess. Cytologic examination of the sputum showed cells consistent with squamous cell carcinoma. Biopsy of a cervical gland, however, showed malignant lymphoma. Bronchoscopy revealed obstruction of the lower part of the right bronchus. Biopsy of material obtained at bronchoscopic examination revealed squamous cell carcinoma.

After the biopsy of the cervical gland, it was natural to assume that the pulmonary lesion represented infiltration by lymphomatous tissue. The smear, however, correctly indicated a second diagnosis, totally unexpected both by the roentgenologist and the clinician.

CANCER OF THE URINARY TRACT

Cancer of the kidney and bladder, even if early, is usually detectable by the classic methods of investigation. Nevertheless, cytologic examination occasionally reveals a malignant process overlooked at endoscopy.

A man of 78 complained of prostatitis and cystitis of ten years' duration. Cytologic examination of the urine sediment showed cancer cells in five smears over a twelve month period, during which time results of cystoscopy were twice negative. In January 1948, a tiny papilloma was seen in the base of the bladder on the left side, biopsy of which showed carcinoma grade IIIB.

I. M., a 60 year old man, complained of hematuria. Biopsy showed chronic and acute cystitis. Clinical diagnosis was benign prostatic hypertrophy. Results of cystoscopy were negative. Urine smears were positive for cancer. Three months later a second biopsy showed carcinoma. A cystectomy was performed.

Statistically, in comparison with examination of other body fluids, examination of the urine has been in our hands the least satisfactory. We have, however, been able to diagnose correctly 71 per cent of bladder carcinomas. Cancer of the kidney has been diagnosed in only 50 per cent of a small series and cancer of the prostate in only 42 per cent. In the urine, moreover, our false positive results have averaged 1 in 10, a figure higher than that occurring in the examination of any other body fluid.

Although the statistical accuracy in examination of urine sediments is not high, we have in a series of 225 cases discovered by this method 3 completely unsuspected cases of cancer, 1 of the kidney and 2 of the bladder.

According to Young [36] in only 1 in 5 cases is prostatic cancer diagnosed in a stage suitable for radical prostatectomy. Herbut [37] examined the prostatic secre-

27. Herbut, P. A., and Clerf, L. A.: Bronchogenic Carcinoma: Diagnosis by Cytological Study of Bronchoscopically Removed Secretions, J. A. M. A. 130:1006-1012 (April 13) 1946.
28. Dudgeon, L. S.: On the Demonstration of Particles of Malignant Growth in Sputum by Means of the Wet-Film Method, St. Thomas's Hosp. Rep. 1:51-65, 1946.
29. Gowar, F. J. S.: Carcinoma of the Lung: The Value of Sputum Examination in Diagnosis, Brit. J. Surg. 30:193-200, 1943.
30. Wandall, H. H.: A Study of Neoplastic Cells in Sputum as a Contribution to the Diagnosis of Primary Lung Cancer, Acta chir. Scandinav. (supp. 93) 91:1, 1944.
31. Herbut, P. A., and Clerf, L. H.: Cancer Cells in Bronchial Secretion, M. Clin. North America 30:1384-1392, 1946.
32. Herbut, P. A.: Personal communication to the authors.
33. McKay, D. G.; Ware, P. L.; Atwood, D. A., and Harken, D. E.: The Diagnosis of Bronchogenic Carcinoma by Smears of Bronchoscopic Aspiration, to be published.
34. Woolner, L. B., and McDonald, J. R.: Bronchogenic Carcinoma: Diagnosis by Microscopic Examination of Sputum and Bronchial Secretions; Preliminary Report, Proc. Staff Meet., Mayo Clin. 22:369-381, 1947.
35. Woolner, J. B.: Personal communication to the authors.
36. Young, H. H.: The Cure of Cancer of the Prostate by Radical Perinial Prostatectomy, J. Urol. 53:188-256, 1945.
37. Herbut, P. A.: Personal communication to the authors.

tion obtained from 450 patients, 54 of whom had prostatic cancer. Cancer cells were correctly recognized in 39 instances, or 85 per cent. It is evident that in examination of prostatic fluid, as in the examination of bronchial and gastric aspirates, the percentage of correct diagnoses by the cytologic method varies directly with the interest and capability of the physician who collects the specimen. For cytologic diagnosis to be effective, the first requisite is that cancer cells be placed on a slide; the second is the recognition of cancer cells in the stained specimen. In cytologic diagnosis, proper collection of the specimen is as important as skill in interpretation.

GASTRIC CANCER

Because, until moderately advanced, cancer of the stomach usually presents no symptoms, discovery of gastric carcinoma in an early stage is rare. Despite the improvements in surgical technic during the last twenty years, little advantage has accrued to the patient with cancer of the stomach. Eighteen years ago 5 of every 100 patients with gastric cancer entering the Massachusetts General Hospital obtained five year cures. A decade later (1940) 7 of every 100 obtained a five year cure.[38] It is still often impossible to decide on roentgenographic evidence whether a given gastric lesion is malignant or not. At the Massachusetts General Hospital during the years 1931-1940, 14 per cent of gastric ulcers clinically (and roentgenologically) considered benign were observed to be malignant, and, conversely, 17 per cent believed to be malignant proved to be benign. The surgeon with the stomach in his hand often cannot determine whether cancer is present or not. It is, therefore, not surprising that in this disease late diagnosis is the rule rather than the exception.

Papanicolaou [39] in 1946 reported the recognition of cancer cells in gastric fluid. The following year Papanicolaou and Cooper [40] published a report on 137 cases, in 27 of which there was gastric cancer. Of the 27, results of cytologic examination were positive in 10, suspicious in 7 and negative in 10. Of smears from 110 patients without cancer, those of only 9 were called suspicious and none positive.

In the Vincent Memorial Laboratory we have studied sediments of gastric fluid from 193 patients. Of 65 patients with gastric carcinoma, positive smears were obtained in 35 (54 per cent). Of 128 patients without cancer, smears were mistakenly reported positive in 3.

While statistically these results are not satisfactory, an individual case not infrequently emphasizes the value of the test in the recognition of gastric cancer and suggests that with improved technic a larger proportion of positive results might be obtained.[41]

S. B., a man of 57, complained of dysphagia of six months' duration. A roentgenogram showed spasm of the esophagus; a second roentgenogram showed no abnormalities. Gastroscopy revealed esophagitis, and a biopsy showed chronic inflammation. Cytologic examination of gastric contents revealed a malignant condition. A repeat gastroscopy showed spasm of the esophagus, and a malignant condition was suspected. At operation extensive cancer of the stomach was observed. Pathologic examination revealed signet ring carcinoma.

A. L., a woman aged 41, complained of regurgitation of nine years' duration and of epigastric pain of four years' duration. A roentgenogram in 1935 had shown a gastric ulcer. Roentgenograms ten years later, in 1945, indicated gastritis. Results of gastroscopy were negative. In 1947 gastroscopy revealed gastritis. One roentgenogram suggested benign polyposis and a second, early in 1948, gastritis. Smears of the gastric fluid were positive for cancer. At operation the surgeon observed evidence indicating gastritis only. Pathologic examination showed adenocarcinoma involving almost the entire mucosa of the specimen.

The next case is an example of the difficulty in recognizing cancer even though the stomach lies in the surgeon's hand.

E. C., 56 years old, suffered for six weeks with pain in the left upper quadrant of the abdomen. Roentgenograms indicated gastric neoplasm. Results of cytologic examination were positive. At operation Dr. Arthur Allen felt a soft movable tumor within the stomach; he expressed the belief that it represented a benign polyp. Only a limited subtotal gastrectomy was performed, and grossly the tumor appeared to be benign. The diagnosis based on pathologic examination was adenocarcinoma with metastasis to regional lymph nodes.

As previously stated, our results in the diagnosis of gastric cancer are so far not statistically satisfactory. However, Graham and Ulfelder from our laboratory [42] have reported the correct diagnosis by smear in 5 cases of resectable gastric cancer, and in 2 extremely early cases of gastric cancer. In a small study group, to be reported later, changes in technic of collection of the gastric fluid have already resulted in a much higher proportion of positive smears. If a majority of early cases are found to be diagnosable by smear, the value of the cytologic method in the control of carcinoma of the stomach will be incontestable.

SUMMARY

The rationale, technic and accuracy of the cytologic method in the diagnosis of cancer is reviewed. It is shown that invisible lesions (cervix), noninvasive lesions (cervix) and tumors inaccessible for visualization or biopsy (lung, prostate) can be diagnosed by a study of exfoliated cells with an accuracy comparable to that of biopsy.

The likelihood of cancer in a patient with a positive smear is so high that this observation cannot be disregarded. A positive smear demands that every possible effort be made to establish the diagnosis. Radical therapy is justified, however, only if confirmatory evidence is obtained. A negative smear should never outweigh other evidence in favor of malignant disease.

While examination of fixed tissue sections remains the final criterion of malignant disease, evidence is presented that in the lung and cervix, and possibly in the stomach and prostate, cancer may be detected earlier by cytologic examination than is possible by any other means.

38. Welch, C. E., and Allen, A. W.: Carcinoma of the Stomach, New England J. Med. 239:583-589, 1948.

39. Papanicolaou, G. N.: Diagnostic Value of Exfoliated Cells from Cancerous Tissues, J. A. M. A. 131:372-378 (June 1) 1946.

40. Papanicolaou, G. N., and Cooper, W. A.: The Cytology of the Gastric Fluid in the Diagnosis of Carcinoma of the Stomach, J. Nat. Cancer Inst. 7:357-360, 1947.

41. Hunter and Richardson (Cytologic Recognition of Cancer in Exfoliated Material from Various Sources [Useful Modifications of the Papanicolaou Technique]), Surg., Gynec. & Obst. 86:275-280, 1947) embedded and sectioned sediments of many body fluids. By their method a high degree of accuracy in the diagnosis of carcinoma of the stomach was obtained.

42. Graham, R. M.; Ulfelder, H., and Green, T. H., Jr.: The Cytologic Method as an Aid in the Diagnosis of Gastric Carcinoma, Surg., Gynec. & Obst. 86:257-259, 1948.

DIGITOXIN

Its Evaluation for Initial Digitalization of the Patient with Congestive Heart Failure

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Several reports[1] have recently appeared concerning the value of digitoxin for the treatment of patients with congestive heart failure. It has been demonstrated[1a] that the cat unit potency of digitoxin has no clinical relationship to that of digitalis leaf. It is essential, therefore, that extensive clinical studies be done to establish the proper dosage and the best methods of administration. Furthermore, since many glycosides are becoming available for clinical use, all should be thoroughly studied before any final decision is made concerning the selection of any particular glycoside as the one of choice. As part of our program, now in progress, for the evaluation of cardiac glycosides, digitoxin has been studied in several ways. Its use for the maintenance of the digitalized state in ambulatory patients has already been reported.[2] The purpose of the present report is to submit our experiences with digitoxin for the initial digitalization of the patient with congestive heart failure.

METHOD OF STUDY

Groups of patients with varying degrees of chronic congestive heart failure[3] were given digitoxin[4] according to one of the following oral methods: (1) a modified Eggleston method[5] consisting of multiple doses, (2) a small daily undivided dose and (3) a single large dose as advocated by Gold and his co-workers.[1cd] All patients were hospitalized and without exception were unselected except for the exclusion of patients with complications such as myocardial infarction, pulmonary disease and glomerulonephritis. None were moribund or considered too ill to be followed adequately after digitalization. With few exceptions, the patients had never previously been given any digitalis preparation, and the few exceptions had not received any for at least three weeks prior to digitalization. The fact that the majority of the patients were digitalized for the first time is considered to be important, since it has been our experience that many patients are more responsive to subsequent digitalizations. If a digitalis preparation is given again within a few weeks, the patient who is being redigitalized may require a smaller dose to produce an adequate therapeutic response. All patients were at complete bed rest from the time of entering the hospital until the cardiac status allowed ambulatory care.

Before digitalization the maximum effect of the usual supportive measures was evaluated in each case. The duration of the control period varied from patient to patient depending on the severity of the heart disease and need for digitalization. Unless the patient's condition did not permit, the patient was observed usually for four to five days, and in some cases as long as two weeks before digitoxin was administered. None of the patients received any mercurial diuretic prior to digitalization. In general, the patients were observed according to the regimen established in previous studies.[6]

DIGITALIZATION BY THE MULTIPLE DOSE METHOD

Thirty-seven patients were given digitoxin according to a multiple dose schedule; i.e., they received an initial large dose, and subsequently at six hour intervals a smaller dose was administered until a definitely sustained therapeutic effect occurred or toxicity was noted. It should be made clear that the usual treatment of a patient with congestive heart failure does not require administration of digitoxin or any digitalis preparation to the point of toxicity. Once a sustained therapeutic effect is achieved a maintenance dose is advocated. However, in order to determine the therapeutic range, all patients were given digitoxin to the point of toxicity, the drug's administration being stopped at the first sign or symptom of its occurrence. The initial dose varied between 0.4 and 1.6 mg., with the greatest number of patients receiving 0.6 mg. Subsequent doses varied between 0.2 and 0.4 mg., with the greatest number of patients receiving 0.3 mg.

The therapeutic dose was ascertained in 27 of the patients and ranged between 0.9 and 4.8 mg., averaging 2.2 mg. In the other 10 patients, the therapeutic dose could not be established either because the minimal degree of congestive heart failure did not allow clearcut clinical evidence of improvement or because it was overshadowed by toxic manifestations. Most of the patients had initiation of improvement within twenty-four hours, but a satisfactory therapeutic effect was not achieved until at least forty-eight hours of digitalization. For each patient there was an optimum therapeutic dose which varied greatly from patient to patient. The size of the initial and subsequent doses did not seem to be material as long as the patient received sufficient digitoxin to be fully digitalized in the period of twenty-four to forty-eight hours. The best dosage scheme was found to be an initial dose of 0.6 mg. and then 0.3 mg. every six hours until the desired therapeutic effect was obtained.

The toxic dose ranged between 1.5 and 9.3 mg. (average 4.1 mg.). The type of toxicity was in no way different from that usually seen with the whole leaf of Digitalis purpurea. Anorexia, nausea and vomiting were commonly the earliest symptoms, but there was no way of predicting which patient would experience the more serious forms of toxicity such as abnormal rhythms and heart block, either concomitant with the mild symptoms or independently. This did not differ in any

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1. (a) Gold, H., Kwit, N. T., and Cattell, M.: Studies on Purified Digitalis Glucosides: I. Potency and Dosage of "Digitaline Nativelle" by Oral Administration in Man, J. Pharmacol. & Exper. Therap. 69: 177 (July) 1940. (b) Gold, H.: Digitalis: Its Action and Usage, M. Ann. District of Columbia 10: 127 (April) 1941. (c) Gold, H.; Kwit, N. T.; Cattell, M., and Travell, J.: Studies on Purified Digitalis Glucosides: IV. The Single Dose Method of Digitalization, J. A. M. A. 119: 928 (July 18) 1942. (d) Gold, H., Cattell, M.; Modell, W.; Kwit, N. T.; Kramer, M. L., and Zahn, W.: Clinical Studies on Digitoxin (Digitaline Nativelle) with Further Observations on Its Use in the Single Average Full Dose Method of Digitalization, J. Pharmacol. & Exper. Therap. 81: 187 (Oct.) 1944. (e) Katz, L. N., and Wise, W.: Oral Single Dose Digitalization with Digitalis Leaf and Digitaline "Nativelle," Am. Heart J. 30: 125 (Aug.) 1945. (f) Digitalis Versus Digitoxin, Conferences on Therapy, New York State J. Med. 45: 1676 (Aug. 1) 1945.

2. Batterman, R. C., and DeGraff, A. C.: Comparative Study on the Use of the Purified Digitalis Glycosides: Digoxin, Digitoxin and Lanatoside C for the Management of Ambulatory Patients with Congestive Heart Failure, Am. Heart J., 24: 663 (Nov.) 1942.

3. Nomenclature and Criteria of Diseases of the Heart, Criteria Committee, New York Heart Association, ed. 4, New York, New York Tuberculosis & Health Association, 1939.

4. The digitoxin used was "digitaline nativelle," available in tablets of 0.1 and 0.2 mg. A generous amount of the glycoside was supplied by the Varick Pharmacal Company, Inc.

5. Eggleston, C.: Digitalis Dosage, Arch. Int. Med. 20: 1 (July) 1915.

6. (a) Batterman, R. C.; Rose, O. A., and DeGraff, A. C.: The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure, Am. Heart J., 20: 443 (Oct.) 1940. (b) Batterman, R. C.; Holman, D. V., and DeGraff, A. C.: The Therapeutic Effectiveness and Potency of Digitanid in the Treatment of Congestive Heart Failure, Ann. Int. Med. 14: 2058 (May) 1941. (c) Rose, O. A.; Batterman, R. C., and DeGraff, A. C.: Clinical Studies on Digoxin: A Purified Digitalis Glycoside, Am. Heart J. 24: 435 (Oct.) 1942.

respect from the toxicity noted with any digitalis preparation. However, the striking observation was the persistence of toxicity. In several patients toxicity persisted for many days, although the mild toxic symptoms usually subsided within forty-eight to seventy-two hours.

SLOW DIGITALIZATION WITH DAILY SINGLE DOSES

Twelve patients who were not acutely ill, so that slow digitalization could be followed without fear of jeopardizing the patient's welfare, were included in this group. The daily dose in all but 2 instances was 0.4 mg. This dose was selected because studies in the ambulatory patient [2] indicated that it is the minimal dose which would allow sufficient cumulation for relatively rapid therapeutic response and yet would be sufficiently high to result eventually in minimal toxicity. Digitalization was achieved in 9 of the 12 patients. A therapeutic response was not discernible in 3 patients, 2 of whom had only a questionable amount of congestive heart failure. The desired therapeutic response was noted in three to six days and required from 0.9 to 2.4 mg. (average 1.7 mg.). This dose is slightly lower than that noted for the multiple dose method, but the two groups are not comparable in terms of severity of congestive heart failure. Since the patients in this group were definitely in less congestive heart failure it is probable that they would require a smaller dose. That this is the most likely explanation can be reasoned from the fact that the average of the therapeutic doses obtained by the multiple dose method in 10 patients with comparable degrees of congestive heart failure is 1.6 mg. This fact again indicates that the patient responds only when an optimum dose level is reached regardless of the size of the initial dose, the subsequent doses and the time interval between doses (six to twenty-four hours). Our evidence favors the slow rate of dissipation of digitoxin; otherwise it would be expected that the daily undivided dose method would require a larger average dose than the rapid type of digitalization.

The toxic dose was obtained in 11 of the 12 patients. One patient was able to tolerate 0.3 mg. for twenty-five daily doses without toxicity. Toxicity was noted in four to twenty days with a dose range of 1.6 to 8 mg. (average 3.8 mg.) and was similar to that noted from the multiple dose method.

SINGLE DOSE METHOD

Gold and his associates [1ed] introduced the single dose method for digitoxin and advocated a dose of 1.2 mg. followed in twenty-four hours by a maintenance dose for all patients regardless of age, weight, sex or degree of heart failure. It was deemed advisable, therefore, to include this method in this study. Eighteen patients with chronic auricular fibrillation in various degrees of congestive heart failure were given a single dose of 1.2 mg. of digitoxin and observed for twenty-four hours to note any signs of clinical improvement. With the exception of 1 patient, who was in severe congestive heart failure, all patients were previously observed for several days to eliminate the possibility of spontaneous clinical improvement with bed rest alone. The data on these patients are summarized in the table.

Adequate digitalization was obtained in only 3 patients (17 per cent). Two of these were in mild failure. Eight patients (44 per cent) showed slight evidence of digitalization as indicated by slowing of the ventricular rate and diuresis, but this response was inadequate for satisfactory clinical improvement. None of these patients would have been considered to be fully digitalized. Seven patients (39 per cent) did not present any clinical effects from the single dose of digitoxin. One patient subsequently died before sufficient digitoxin could be administered, while in another patient an additional 2.1 mg. in divided doses was also insufficient, although a complicating acute pulmonary disease occurring subsequent to initial digitalization may have been the responsible factor for death.

Since the claim [7] is made that "full digitalization" is possible with the single dose, an effort was made to determine the exact level of digitalization attained. The patient was "titrated" by administering a small dose of digitoxin at six hour intervals, twenty-four hours after the initial dose, until a satisfactory therapeutic response was obtained, and then continuing until minor signs of toxicity occurred. Eleven patients required 0.4 to 3.3 mg. (average 1.6 mg.) more than the initial 1.2 mg. to achieve a good therapeutic effect. The therapeutic dose in these patients ranged between 1.6 to 4.5 mg., averaging 2.7 mg. If the three patients who responded to 1.2 mg. are included the average therapeutic dose becomes 2.2 mg. An additional 0.9 to 6.9 mg. (average 3.8 mg.) was required to achieve toxicity. The toxic dose varied between 2.1 and 7.1 mg., averaging 4.6 mg.

COMMENT

The response of a patient to an optimum dose of any digitalis preparation depends on several factors, the most important of which are (1) the degree of congestive heart failure, (2) the theoretical maximum improvement possible with the underlying heart disease and (3) the precipitating cause of the congestive heart failure. This optimum dose is specific for each patient and it cannot be predicted. It also varies in the same patient from time to time as conditions change. The administration of an average dose for the treatment of any individual patient is not in the best interest of the patient because of the possibility that such treatment may result in incomplete digitalization or toxicity. The so-called average dose is selected because of the low incidence of toxic manifestations which it may produce. The possibility of toxicity following the administration of such an "average" dose is, therefore, not great. However, toxicity may occur and in the rare hypersensitive patient this may be serious. The primary object in adequate digitalization is to restore cardiac efficiency as quickly as possible. The "average" dose may act as a rough guide for digitalization, but it should not be relied on to digitalize completely any individual patient. This holds true particularly for the single dose method of digitalization with digitoxin. Only 3 of our 18 patients had a satisfactory therapeutic response with this method. It was subsequently necessary in 11 of the patients to administer an additional 33 to 275 per cent (average 133 per cent) of the original dose to obtain a therapeutic digitalis effect. In view of our experiences with the multiple and daily undivided dose methods, this was to be expected. The administration of a large initial dose has only the advantage that the total optimum therapeutic dose may be obtained a few hours sooner. If the optimum dose is exceeded but is still short of a toxic dose, digitoxin will not produce any earlier or greater response than would be produced by the optimum dose itself. It is important, however, to recognize that no satisfactory therapeutic response will be noted until the optimum dose for the individual patient is reached. This point should be arrived at as cautiously as possible because toxicity with digitoxin

7. Gold,[1b] Gold and others.[1c-d]

Digitalization of Hospitalized Patients with a Single Dose of 1.2 Mg. of Digitoxin Orally

Patient	Age	Sex	Diagnosis*		Degree of Congestive Heart Failure†	Weight in Pounds	V.R.‡ Before Treatment	Effect	V.R. 24 Hr. After Single Dose 1.2 Mg. Digitoxin Orally	Dose of Digitoxin in Mg. Administered Every 6 Hours		Additional Doses of Digitoxin Required for Satisfactory Therapeutic Effect	Additional Mg. of Digitoxin Required for Satisfactory Therapeutic Effect	Total Dose in Mg. Required for Satisfactory Therapeutic Effect	Additional Mg. of Digitoxin Required for Toxicity	Total Dose in Mg. Required for Toxicity	Comments
1	63	Male	Arteriosclerotic	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	152	130-152	Slight diuresis with loss of 3½ pounds of edema fluid	116-120	0.3	4	1.2	2.4	5.2	6.4	
2	60	Male	Hypertension, rheumatic fever (inactive)	Enlarged heart, mitral stenosis, mitral insufficiency	AF	+++	183	136-140	Diuresis with loss of 5 pounds of edema fluid	117	0.3	4	1.2	2.4	3.0	4.2	V.R. not controlled until 2.4 mg.; satisfactory diuresis not obtained until 3.3 mg. were administered
3	64	Male	Hypertension, arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	++	129	130-140	None noted	150	0.3	3	0.9	2.1	0.9	2.1	No therapeutic response was noted until patient was toxic
4	52	Male	Hypertension, arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	143	128-140	None noted	108+	0.3	6	1.8	3.0	3.3	4.5	Six hours after initial dose, patient required aminophyllin parenterally, mercupurin and sedation for relief
5	61	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+	144	130-170	Relief of dyspnea and orthopnea; no diuresis	82-108	0.3	11	3.3	4.5	5.7	6.9	Diuresis and control of V.R. occurred only after 3 days of continuous therapy
6	28	Male	Rheumatic fever (inactive)	Enlarged heart, mitral stenosis, mitral insufficiency	AF	+	170	130	Control of V.R.	84	0.3	—	—	1.2	1.2	2.4	
7	67	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	++	111	114-126	None noted	114	0.3	4	1.2	2.4	2.4	3.6	
8	67	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+	180	96-121	Slight slowing of V.R.	90	0.3	5	1.5	2.7	5.4	6.6	
9	60	Male	Hypertension, arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	160	96-109	Diuresis of 4 pounds and control of V.R.	80	0.3	—	—	1.2	4.5	5.7	
10	55	Male	Hypertension	Enlarged heart	AF	+++	188	132-156	Slight slowing of V.R.	118	0.3	2	0.6	1.8	3.9	5.1	Diuresis and control of V.R. did not occur until 1.8 mg. was given
11	85	Male	Hypertension, arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	—	120-136	Slight slowing of V.R.	100	0.3	10	3.0	4.2	6.9	7.1	Patient had massive anasarca. V.R. was not controlled until 4.2 mg. of digitoxin was given
12	63	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis coronary sclerosis	AF	+++	150	108-140	None noted	108							Required mercurial diuretic 24 hours after single dose to obtain relief
13	75	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	++	179	100-116	Slight slowing of V.R.	90	0.3	4	1.2	2.4	0.3+	7.5+	Toxic dose not obtained since patient requested discharge from hospital
14	84	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+	108	100	V.R. controlled; no clinical improvement	84	0.2	2	0.4	1.6			Patient received an additional 1.6 mg. without toxicity
15	65	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	202	160	No clinical improvement	120							Patient died on second day; could have sufficient digitoxin could be administered; had received additional 0.6 mg.
16	65	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+	104	144	No clinical improvement	128	0.3						No therapeutic response noted after additional 2.1 mg.; patient died, with acute pulmonary disease 4 days after initiating therapy
17	66	Male	Hypertension, arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+	145	126-147	V.R. controlled and diuresis	86				1.2			
18	80	Male	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	172		None noted	132	0.2				1.2	2.4	

*According to the Nomenclature and Criteria for Diagnosis of Diseases of the Heart, Ed. 4, 1939, New York Heart Association.

†Ascertained by general appearance of patient and clinical response during a preliminary period of control.

‡Ventricular rate.

‖ Auricular fibrillation.

may be severe and it may persist for many days. It is for these reasons that we recommend the multiple dose method.

Our results and conclusions are at variance with those reported by Gold and his associates [8] and more recently by Katz and Wise [1e] but are in accord with the experiences of Stewart.[9] Reasons for this variance are not at once apparent, but they may be related to the selection of patients included for study. The original group of patients used by Gold and his co-workers [1a] consisted of 14 subjects with regular sinus rhythm and 16 subjects with auricular fibrillation. The dose was determined by comparing the alterations of the S-T segment and T waves in the electrocardiogram produced by digitoxin and digitalis leaf in patients with regular sinus rhythm, while the ventricular rate was followed in the patients with auricular fibrillation. The two methods yielded similar results. The conclusion was reached that "the full digitalizing dose (to a point bordering on minor toxic effects) given at one time lies, in the average adult between 1 and 1.25 mg. or 2.4 to 3 cat units." However, only 2 of the patients with regular sinus rhythm and 8 of the patients with auricular fibrillation were in congestive heart failure, and in these the degree of failure was not mentioned. This may have been responsible for the low dose of digitoxin reported. The use of the electrocardiogram as a means of gaging the effective dose of digitalis is open to several objections. First, the changes in the S-T segment and T wave are merely manifestations of digitalis action which usually occur simultaneously with other effects of digitalis such as slowing of the ventricular rate or improvement in muscular efficiency. The occurrence of any one of these effects may be independent of the others, so that a patient may have satisfactory clinical improvement without electrocardiographic changes. Similarly, electrocardiographic changes may be observed without concomitant clinical improvement. That the majority of patients will have the electrocardiographic changes occurring in proportion to the dose administered may be true for digitoxin and digitalis leaf, but there is no such correlation when other glycosides such as digoxin and lanatoside C [10] are used. A similar degree of improvement of cardiac status and maintenance could be achieved with either of these glycosides, even though electrocardiographic changes are not as great as when digitoxin or digitalis leaf are used. Second, as a guide for digitalization, the changes in the electrocardiogram cannot replace the need for establishing the dose clinically in patients. This fact has also been noted by Gold [9] who has stated that "It takes about three times as much digitalis to bring about the full therapeutic effects in heart failure as to produce changes in the T wave, and there are some patients who show negligible changes in the T wave with doses of the drug sufficient to control heart failure, while others may show advanced T wave changes with doses of the drug which cause negligible effects in heart failure." Since the frequency distribution curve [1b] obtained with the effect of digitalis on the T wave would suggest 1.2 mg. of digitoxin as the "average dose," according to the foregoing statement this dose is approximately one third that required for full therapeutic effects. This more closely approximates the figure obtained by us. Nevertheless, the same investigators continue to claim [9] that 1.2 mg. is the "average full digitalizing dose."

8. Gold and others,[1c-d] Footnote [1].
9. The Dose of a Drug, Conferences on Therapy, Am. J. Med. 2:296 (March) 1947.
10. Studies still in progress.

Gold and his associates [1c] treated 213 patients with varying degrees of heart failure including patients with auricular fibrillation and regular sinus rhythm. However, it is not clear whether these patients were being treated for the first time or were being redigitalized. In view of the statement "they had been without digitalis for at least three weeks" it would appear that the latter was most likely. It has been our experience that such patients often require a much smaller dose of a digitalis preparation to obtain adequate digitalization. The same holds true for the report by Katz and Wise.[1e] Not only was their study performed on previously digitalized patients, but only 5 of their 15 patients presented any congestive heart failure. Futhermore, since their patients were kept at complete bed rest only on the day of digitalization, they did not exclude the possibility of response to bed rest alone.

The doses of digitoxin advocated by Gold and his associates for both initial digitalization and maintenance are not in accord with clinical experiences for the treatment of congestive heart failure. It is well known that a definite correlation exists between the dose required for initial digitalization and the dose required for maintenance. As a rule the larger the initial dose, the larger the maintenance dose; yet 1.2 mg. of digitoxin, which is relatively a small dose, is advocated for initial digitalization, while 0.2 mg., a high dose, is recommended for maintenance. Perhaps this relatively high daily dose is required to supplement the therapeutic effects initiated with the single dose of 1.2 mg. and what is observed is not maintenance but cumulative digitalization. Since between 50 and 60 per cent of patients [2] can be maintained without toxicity on this high daily dose of digitoxin, it might have been assumed that this dose is a satisfactory maintenance dose. However, it is usually twice the minimal maintenance dose and approximately 30 per cent of patients [2] taking this dose for ten to twelve weeks will manifest signs and symptoms of toxicity.

We must disagree with the statement [1d] that the incidence of toxic effects when the single dose is given to a large number of patients is more important than the incidence of satisfactory digitalization. It is always possible to determine the largest single dose which will result in the smallest incidence of toxicity, but unless that dose results in satisfactory digitalization, all that has been accomplished is that a safe dose has been determined. An "average" dose may aid in achieving the optimum therapeutic dose, but it can not be relied on to produce adequate digitalization.

It has been frequently emphasized that the so-called single digitalizing dose of digitoxin produces less local gastrointestinal irritation than an equivalent amount of digitalis leaf. However, this is the case only when one compares the administration of a single large dose of digitoxin with an equivalent dose of digitalis leaf. The assumption is made that if digitalis leaf were not so irritating, a single large dose of the leaf would be preferable for digitalization. However, sufficient clinical experience with digitalis leaf has favored the administration of small multiple doses.[5] The object of this method is to have a better control of dosage and to assure a more effective and safe digitalization rather than to avoid local gastrointestinal symptoms. With usual doses of digitalis leaf, the factor of gastrointestinal irritation is negligible.

We believe that the factor of absorbability from the gastrointestinal tract is also being overemphasized. It is desirable to know that a particular glycoside is ab-

sorbed in sufficient amounts to exert a therapeutic effect and whether this effect can be achieved with a fair degree of dependability with a prescribed dose. However, it seems to us that this is of major consideration in the establishment of a maintenance dose but is not so significant in initial digitalization. The individual patient is given a digitalis preparation at regular intervals until a desired therapeutic effect is achieved or toxicity results. As long as absorption occurs and the intervals are so spaced that the rate of dissipation is not too rapid, sufficient cumulation will occur. A more completely absorbed preparation does not result in any faster digitalization unless that particular glycoside has a short latent period of action. This is not so with digitoxin. Clinically the time taken for digitalization orally with digitoxin is no shorter than that observed by the oral route with digitalis leaf, digoxin and other glycosides. On the other hand, variability in absorption may play a role in establishment of the maintenance dose.[2] The method of comparing the effects of a single intravenous dose of a glycoside with a single oral dose as a guide to completeness of absorption must take into consideration the following factors:

1. A determination of the minimum optimum therapeutic dose for each method of administration. This is important because, as stated before, considerably more of a digitalis preparation can be given beyond the optimum dose with the same therapeutic effect. We have found no evidence in the literature that such a comparison has ever been made with digitoxin. Thus the results of giving a single dose of 1.25 mg. of digitoxin orally and parenterally may be identical. It has not been demonstrated, however, that the patient would not respond to an equivalent degree to a smaller dose given parenterally. Within certain limits the results would be identical because the patient would respond to a dose as long as it is optimum or above. If absorption is identical as determined by effects, then the toxic dose should also be identical. Whereas 2 mg. of digitoxin orally results in minor toxicity in 32 per cent [1a] of cases, there is good reason to believe that the incidence and severity of the toxicity with this dose would be considerably higher by the intravenous route.

2. The latent period and rate of dissipation. A rapidly acting glycoside like digoxin will produce its effects within a few minutes if the concentration reaching the heart muscle is within optimum limits. However, if the drug is rapidly dissipated, the slower rate of absorption from the gastrointestinal tract does not allow sufficient cumulation with a single dose to attain the same level of concentration at the heart muscle to give at any instant of time an effect comparable to the intravenous route. The drug may be completely absorbed, but this is overshadowed by its rate of dissipation. Digitoxin, on the other hand, is so slowly dissipated that an oral dose will attain an effective concentration comparable to that achieved with the same parenteral dose. With slowly dissipated glycosides which possess comparatively long latent periods of action, a sufficient concentration may be eventually reached to produce the same effect as the parenteral dose. With the more rapidly dissipated glycosides such as digoxin and lanatoside C, which possess a comparatively short latent period, a single dose will produce a strong effect almost immediately on intravenous administration, but when the same dose is given orally a similar effect can never be reached.

Digitoxin when used properly fulfils the criteria for a satisfactory preparation of digitalis. However, one must be extremely cautious in its use because of the possibility of toxicity which on the basis of an extremely slow rate of dissipation may be serious and prolonged.

From our studies, digitoxin offers no particular advantage over digitalis leaf for the usual treatment of a patient with congestive heart failure.

The disadvantages in the use of digitoxin as discussed in this paper and our clinical studies with this and other purified digitalis glycosides [2] lead us to conclude that digitoxin is not the one of choice.

SUMMARY AND CONCLUSIONS

Three methods for the oral administration of digitoxin for the initial digitalization of the patient with congestive heart failure are compared. Regardless of the method used, an optimum dose is required for any specific patient before a therapeutic response is attained.

The average therapeutic dose for the multiple dose method was found to be 2.2 mg. as compared with 1.7 mg. for the single undivided daily dose and 2.7 mg. for the single large dose with supplementary administration of digitoxin.

The average toxic dose for the multiple dose method was found to be 4.1 mg. as compared with 3.8 mg. for the single undivided daily dose and 4.6 mg. for the single large dose with supplementary digitoxin administration.

"Full digitalization" was not considered to have been adequately obtained with the single large dose of 1.2 mg. of digitoxin since a satisfactory digitalization was obtained in only 17 per cent of the patients and 0.4 to 3.3 mg. (average 1.6 mg.) additional digitoxin had to be administered before the optimal therapeutic response was reached.

Reasons are presented for selection of the multiple dose method as the one of choice for administering digitoxin.

Digitoxin offers no particular advantage over digitalis leaf for the routine treatment of the patient with congestive heart failure. Because of its slow dissipation and the possibility of prolonged and severe toxicity, digitoxin is not in our opinion the glycoside of choice.

Retinitis Pigmentosa.—One of the common causes of blindness is retinitis pigmentosa. Ten years ago it could be said that in some pedigrees this disease was transmitted as a dominant, in others as a recessive of the ordinary type, occasionally as a sex-linked recessive. In 1936 I argued that some pedigrees showed partial sex-linkage . . . We can now say tentatively that one of the genes, the abnormality of which causes this condition, is carried in that segment of the sex chromosomes of which women possess two, and men only one; another, which may give dominant or recessive mutants, in that segment of the same chromosomes of which both sexes possess two; while other such genes, how many we do not know, are carried in the other chromosomes. It is reasonably sure that they control different processes. And this is borne out by the fact that the partially sex-linked recessive type is never associated with deafness, while one of the autosomal recessives is so associated.

Pathologists will have to work out the aetiology of the different genetical types. They can hardly hope to do so until they are distinguished, if, as seems probable, each gene controls a different process. And just as the methods for the cure of bacillary and amoebic dysentery are very different, so it is unlikely that the same therapeutic measures will succeed against diseases, however similar in their symptoms, which are due to different genes.—Haldane, J. B. S., *Proceedings of The Royal Society*, June 1948.

JARISCH-HERXHEIMER REACTION IN EARLY SYPHILIS

Treated with Crystalline Penicillin G

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The transient intensification of the symptoms and signs of early syphilis shortly after the institution of treatment (the Jarisch-Herxheimer reaction) has been repeatedly observed after the administration of mercury, bismuth and arsenical drugs. In 1943 Mahoney, Arnold, and Harris [1] first described the same febrile and cutaneous reactions in patients with early syphilis within eight hours after the initial injection of commercial penicillin. Subsequently a number of observations concerning the various manifestations, the specificity, the incidence and the severity of this reaction in early syphilis treated with commercial penicillin were reported. No attempt is made here to compare the frequency and severity of Herxheimer reactions after the administration of bismuth and arsenical preparations with those occurring after administration of penicillin.

Between July 1946 and June 1947 a large group of patients with early infectious syphilis were treated with crystalline penicillin G in twenty cooperating clinics, including the Johns Hopkins Hospital, under the direction of the Syphilis Study Section of the United States Public Health Service. From case reports sent to the Central Statistical Unit by those clinics the incidence of this reaction was determined. A group of patients with relapsing early syphilis was studied at the Johns Hopkins Hospital to clarify the possible prognostic value of this reaction. The relationship of the reaction to the dosage of crystalline penicillin G was determined in order to evaluate the possible benefit to be derived from small initial doses of penicillin, which have frequently been given in an effort to prevent the reaction. The relationship of penicillin dosage to febrile reactions and also to the disappearance time of Treponema pallidum was studied with the hope of obtaining further information concerning the theoretic nature of the Herxheimer reaction.

MANIFESTATIONS

The usual symptoms and signs of the Herxheimer reaction in early syphilis include any one or combination of the following observations:

1. Systemic or febrile phase of the reaction: chilliness, elevation of temperature, malaise, headache and nausea.

2. Focal or cutaneous phase of the reaction: edema or pain in the primary ulcer, enlargement of, or pain in, the regional lymph nodes, intensification of a secondary eruption or of other local lesions or the development of generalized roseola in primary syphilis. All of these signs and symptoms occur between four and forty-eight hours after the initial injection of penicillin. Therefore, the Herxheimer reaction may be classified as one of the "immediate reactions" to penicillin, in contrast with "delayed reactions."

The manifestations of the reaction vary. One patient with primary syphilis may have a generalized macular eruption and no fever; another may have fever with no focal signs; a third may have an elevation of temperature with no subjective symptoms. Of the various forms of the reaction the elevation of temperature may be measured most accurately.

In addition to these frequent manifestations of the Herxheimer phenomenon, focal reactions of the cornea have been described during penicillin therapy in syphilitic uveitis.[2] Intensification of the inflammatory reaction in papular lesions of the cornea in patients with secondary syphilis was observed under the corneal microscope. This increase in the number of inflammatory cells associated with haziness and corneal precipitates was described as a part of the "histologic phase" of the Herxheimer reaction. Similar studies of the cutaneous lesions of secondary syphilis by the microscopic examination in repeated biopsies have revealed an increased inflammatory reaction in four to six hours after the administration of penicillin.[3]

The Herxheimer reaction has been observed after intramuscular,[4] intravenous [5] and oral [6] administration of penicillin in early syphilis. It has been noted following the use of peanut oil and wax suspensions [7] and of aqueous solutions of penicillin.

Scott and Clark [8] have reported the development of a transient nephrotic syndrome in a patient with early syphilis treated with penicillin, which they considered an unusual manifestation of a Herxheimer reaction. There is little evidence presented for this assumption, since the complication developed on the thirteenth day after the first injection of penicillin and on the fifth day after the completion of treatment. This represents a "delayed reaction."

SPECIFICITY

An evaluation of the specificity of the Herxheimer reaction in response to penicillin in early syphilis depends on accurate data concerning the incidence of febrile and cutaneous reactions following the administration of penicillin in other diseases.

In the treatment of primary and secondary yaws with penicillin, both febrile and cutaneous reactions have been reported.[9] Temperatures of 100 to 104 F (37.8 to 40 C.) occurred in one half of 200 patients from two to eight hours after penicillin therapy was started. Thus, the Herxheimer reaction has been observed in this closely related spirochetal disease.

Herxheimer reactions have not been reported in a wide variety of acute generalized infections treated with penicillin. Since most of the patients in these

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9. Swindelle, J. H.; Rein, C. R.; Sternberg, T. H., and Sheldon, A. J.: Preliminary Report on the Evaluation of Penicillin in the Treatment of Yaws, Am. J. Trop. Med. 26: 311-318 (May) 1946. Ledgren, R. C.: Yaws Treated with Penicillin: Report of a Case, U. S. Nav. M. Bull. 42: 1025-1030 (Nov.) 1944.

groups were already febrile, it was difficult to exclude the possible occurrence of secondary fever superimposed on an underlying febrile course. However, febrile reactions to penicillin among an analogous small group of cases of secondary syphilis with fever have been observed.[9] In such cases, this reaction could be clearly delineated only when there was a maximal febrile response.

Patients with uncomplicated gonorrhea represent a satisfactory control group for the observation of possible febrile reactions to penicillin therapy, since these patients are usually afebrile. In a report[10] of the results of the treatment with penicillin of 675 hospitalized women with gonorrhea, a mild rise in temperature during treatment was noted in only 2 patients, and both of these women had concomitant early syphilis. The frequency of observations of temperature in this group of cases was not stated. Thus, although adequate control groups are not available, it is said that early febrile reactions to the administration of penicillin to patients with nonspirochetal infections are rare, if not nonexistent. The point requires further investigation.

In contrast with the apparent specificity of the febrile type of response, immediate cutaneous reactions to the administration of penicillin have been observed in patients with nonsyphilitic infections. Focal and generalized cutaneous reactions, occurring between ten and twenty hours after the injection of penicillin, have been noted in 18 (25 per cent) of 73 patients with various types of dermatitis (eczematoid dermatitis, atypical lichen planus and undifferentiated dermatitis).[11] Two types of reaction occurred, either a local exacerbation of the cutaneous condition, with hyperemia, pruritus and exudation of serum, or a generalized erythematous eruption. It was suggested by the authors, on the basis of results of cutaneous tests with penicillin and trichophytin antigen, that these reactions might be due to sensitization from a past or present fungous infection. Similar reactions in lesions of fungous origin have been described after the administration of penicillin.[12] The same increased inflammatory reactions which have been reported in syphilitic uveitis were also noted in 25 per cent of 36 patients with nonsyphilitic uveitis following the institution of penicillin therapy.[2] Thus, focal reactions to the administration of penicillin do occur in nonsyphilitic patients, and these might be clinically indistinguishable from the focal Herxheimer reactions in early syphilis.

RESULTS

Incidence.—With commercial penicillin, febrile reactions have been observed in 30 to 70 per cent of adults with early syphilis,[6b-d] and in 43 to 55 per cent of infants with congenital syphilis.[13] The incidence of cutaneous reactions has not been accurately determined. Although the phenomenon has been reported to the Central Statistical Unit by the cooperating clinics in from 2 to 10 per cent of cases, this certainly is an underestimate of the true incidence of focal reactions. The "histologic phase" of the reaction has been observed in 70 per cent of patients with syphilitic uveitis.[2]

The incidence of febrile reactions following the administration of crystalline penicillin G[14] was studied among a group of 939 patients with early infectious syphilis treated in twenty cooperating clinics. These patients were treated with initial doses of 25,000 to 50,000 Oxford units and with total doses of 2,400,000 to 4,800,000 Oxford units of penicillin administered intramuscularly. Temperatures were recorded every four hours.

TABLE 1.—*Relationship of the Incidence of Febrile Reactions to the Race and Sex of Patients with Early Syphilis Following Treatment with Crystalline Penicillin G*

Race	Total No. Treated	No. with Febrile Reactions	Percentage with Febrile Reactions
White	186	85	46
Negro	753	299	40
Total	939	384	41
Sex			
Male	498	207	42
Female	441	177	40
Total	939	384	41

Of this group, 384 (41 per cent) had febrile reactions (table 1). No significant race or sex differences in the incidence and severity of febrile reactions were demonstrated (table 1).

Relationship to the Stage of Early Syphilis.—Febrile reactions have been reported to occur when penicillin is administered during the incubation period of syphilis. Two patients[15] have been observed in whom elevations of temperature were recorded during penicillin therapy for uncomplicated gonorrhea. At the time of treatment, their reactions to serologic tests for syphilis were negative. Secondary syphilis developed in these patients on the twenty-fifth and thirty-fifth days after penicillin therapy. Similar observations[16] concerning the possible occurrence of the Herxheimer reaction during the incubation period of syphilis have been reported of 66 patients with early syphilis who gave a history of gonorrhea treated with penicillin during the possible incubation period of syphilis. Of these 66 patients, 18 gave a history of fever or chilly sensations accompanying penicillin therapy for gonorrhea. Thus, there is presumptive evidence that Herxheimer reactions to penicillin do occur during the incubation period of syphilis. However, it is not known how early in the incubation period such reactions occur nor how frequently they develop.

The relationship of the incidence and severity of febrile reactions to the stage of early syphilis among 800 patients treated with crystalline penicillin G is shown in table 2. Febrile reactions were observed with equal frequency and severity in patients with seronegative primary, seropositive primary and secondary syphilis. The incidence of this phenomenon was 39 to 43 per cent in these three groups of cases. The height of the febrile response was just as great in the group of patients with seronegative primary syphilis as it

10. Thomas R. B., and Meyer, E.: Penicillin in the Treatment of Gonorrhea: Results with Six Hundred and Seventy Five Women, J. Ven. Dis. Inform. **26**:94-98 (May) 1945.
11. Kolodny, H. H., and Dexbeil, E.: Reactions in Penicillin Therapy, J. A. M. A. **130**:1058-1061 (April 20) 1946.
12. Lamb, J. H.: Allergic Reactions During the Administration of Penicillin, Arch. Dermat. & Syph. **52**:93-95 (Aug.) 1945.
13. (a) Platou, R. V.; Hill, A. J., Jr.; Ingraham, N. R.; Goodwin, M. A.; Wilkinson, R. E., and Hanson, A. E.: Effect of Penicillin in the Treatment of Infantile Congenital Syphilis: Further Observations, Am. J. Dis. Child. **71**:635-648 (Dec.) 1946. (b) Herman, A., and Vampolsky, J.: Treatment of Infantile Congenital Syphilis with Penicillin, Am. J. Dis. Child. **71**:306-312 (May) 1946.
14. The crystalline penicillin G used in these studies was supplied by the Commercial Solvents Company, lot numbers 46042605 and 46052605 and potency 1500-1540 units per milligram.
15. (a) Atcheson, D. W.: Secondary Syphilis Following Penicillin Therapy of Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **29**:423-425 (July) 1945. (b) Leifer, W., and Martin, S. P.: Effect of Penicillin in the Course of Early Syphilis, J. A. M. A. **130**:202-205 (Jan.) 1946.
16. Fraser, S.; Cutler, J. C., and Levitan, S.: Masking of Early Syphilis by Penicillin Therapy in Gonorrhea, J. Ven. Dis. Inform. **27**:174-177 (July) 1946.

was in the groups of patients with seropositive primary and secondary syphilis (table 2).

Relationship to Relapse.—The occurrence of Herxheimer reactions in relation to relapse was studied among 395 patients with early syphilis treated with commercial penicillin at the Johns Hopkins Hospital. In this group there were 56 cases of mucocutaneous relapse. Each of these patients with relapse had an initial early syphilitic infection followed by a relapse

TABLE 2.—*Relationship of the Incidence and Severity of Febrile Reactions to the Stage of Early Syphilis in Patients given Crystalline Penicillin G*

Type of Febrile Reaction	Sero-negative Primary Syphilis		Sero-positive Primary Syphilis		Secondary Syphilis		Total	
	Number Treated	Percentage	Number Treated	Percentage	Number Treated	Percentage	Number Treated	Percentage
Fever—All Grades	46	39	92	43	195	42	333	42
Grade I (0 to 1 F. rise)	23	19	36	17	113	24	172	22
Grade II (1 to 2 F. rise)	9	8	23	11	49	11	81	10
Grade III (2 to 7 F. rise)	14	12	33	15	33	7	80	10
No febrile Reaction	71	61	124	57	272	58	467	58
Total	117	100	216	100	467	100	809	100

*Of the 939 patients presented in table 1, there was complete data concerning the stage of early syphilis for 800.

treated with a second course of penicillin. The total doses of penicillin varied from 600,000 to 4,800,000 Oxford units. Most of the medicaments given to this group consisted of many different lots of commercial penicillin from several manufacturers. A few of the patients with relapse were treated with crystalline penicillin G. Temperatures were recorded rectally every four hours, and a temperature above 100 F. (37.8 C.) was considered to represent a febrile reaction.

In the 395 patients, 188, or 48 per cent, had Herxheimer reactions. Among those 188 patients with febrile reactions, relapsing infections occurred in 28, or 15 per cent. Among the 207 patients without reactions, relapses occurred in 28, or 14 per cent. The duration of follow-up study in these two groups was similar. Thus, in these patients the relapse rates were approximately the same in patients who did and who did not have Herxheimer reactions during the first course of treatment.

Of the 56 patients with relapse, 28, or 50 per cent, had febrile reactions with the first course of treatment, and 21, or 38 per cent, had reactions at the time of retreatment. There was no tendency for Herxheimer reactions to recur in the same half of this group. All combinations of occurrence of febrile response were noted with similar frequency: febrile reactions with both treatments (10 cases), no febrile reaction with either treatment (17 cases), fever with the first treatment only (18 cases) and fever with the second treatment only (11 cases).

Relationship to Dosage.—In the few observations concerning dosage which have been reported in early syphilis[17] and in infantile congenital syphilis,[12b] no relationship between the incidence of reactions and the size of the initial dose in a range of 1,000 to 50,000 Oxford units of penicillin has been observed.

In order to obtain more detailed information on this point, a group of 121 patients with early infectious syphilis was studied at the Johns Hopkins Hospital. In each case the diagnosis was established by the demonstration of T. pallidum. Those with fever prior to treatment were excluded from the study. The initial doses administered intramuscularly to these patients varied from 1 to 120,000 Oxford units of penicillin per kilogram of body weight. In those patients who received more than a single dose within the first twenty-four hours, the amount given during the first six hours of treatment was arbitrarily chosen as that amount responsible for the Herxheimer reaction (table 3). Temperatures were recorded rectally every two hours, and a rise above 100 F. (37.8 C.) was considered significant.

TABLE 3.—*Relationship of the Incidence of Febrile Reactions to the Dosage of Crystalline Penicillin G Administered to 121 Patients with Early Syphilis*

Penicillin Dosage given in First 6 Hours	No. of Patients	No. with Febrile Reactions	Percentage with Febrile Reactions
Mg. Kg. Units/Kg.			
13-80* 20,000 = 120,000	9	5	56
2.6† 4,000	34	16	47
1.3† 2,000	22	12	55
0.078‡ 57 =			
0.075 112	18	8	44
0.013 20	10	4	40
0.007 10	4	4	40
0.007* 5	8	0	0
0.0007* 1	10	0	0

*Single dose only in the first forty-eight hours.
†Therapeutic doses repeated every two hours.
‡Large divided doses in the first six hours and no further penicillin for forty-eight hours.

The incidence of febrile reactions over a wide dosage range (10 to 120,000 units per kilogram of body weight) of penicillin varied from 40 to 56 per cent, with no definite trend in relation to dosage. However, when doses of penicillin of less than 10 Oxford units per kilogram of body weight were given, febrile reactions were no longer observed.

Pattern of Fever.—The pattern of the febrile response was studied in the 49 patients who had shown Herxheimer reactions (table 3). Since temperatures had been recorded every two hours in this group, detailed observations of the time of onset, height and duration of fever were available. These factors were analyzed in the following three groups: 5 patients who received large initial doses, 28 patients who received average therapeutic doses and 16 patients who received small doses of penicillin (table 3).

The temperature curves of 28 patients with febrile reactions in response to average therapeutic doses of penicillin (2,000 to 4,000 units per kilogram of body weight) were studied. The average temperature curve of this group is shown in figure 1. The febrile responses followed a uniform temporal pattern, with the height of the fever as the chief variable. The earliest elevation of temperature occurred four hours after injection. By six hours 72 per cent of the group had febrile rises above 100 F. (37.8 C.), and at eight hours 90 per cent of them showed a rise in temperature. The maximal elevations were recorded between six and ten hours

17. Footnote 4a. Olansky, S.: The Herxheimer Reactions of Relatively Small Doses of Penicillin, J. Ven. Dis. Inform. **28**: 26-27 (Feb.) 1947.

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194

after injection in 90 per cent of the group. In 2 cases the maximal febrile responses occurred between twelve and sixteen hours after injection. All of the temperature recordings were normal within twenty-four hours after the first injection.

The average temperature curves of 5 patients with febrile reactions following large initial doses (20,000 to 120,000 units per kilogram of body weight) and of 16 patients given small initial doses (10 to 112 units per kilogram of body weight) of penicillin are presented in figure 1 for comparison with the group given therapeutic doses. Over this wide dosage range the pattern of the febrile reaction did not change. The earliest onset of fever was four to six hours after the injection was given, with the largest as well as with the smallest doses of penicillin which produced a reaction. The maximal elevations of temperature were recorded between six and ten hours after the injection was given in each of these groups, and the average heights of the fever (101.5 to 102 F. [38.7 to 38.9 C.]) were approximately the same. All of the temperature recordings were normal within twenty-four hours after the first injection over this dosage range. The individual maximal temperature recorded in the large initial dosage range was 103.4 F. (39.7 C.) at eight hours after the injection was given; in the therapeutic dosage range, 105 F. (40.6 C.) after six hours, and in the small dosage range, 104.2 F. (40.1 C.) after six hours.

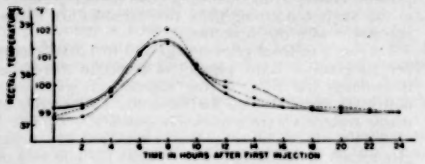

Fig. 1.—Average febrile reactions following the use of crystalline penicillin G in early syphilis in relation to initial dosage. (The broken line represents reactions to doses of 20,000 to 120,000 units per kilogram of body weight [5 cases]; the unbroken line represents reactions to doses of 2,000 to 4,000 units [28 cases], and the dotted line represents reactions to doses of 10 to 112 units [16 cases].)

The similarity of the pattern of fever in response to small doses and also to therapeutic doses of penicillin is further illustrated in figures 2 and 3.

Relationship to Disappearance of T. Pallidum from Lesions.—Observations were made on the relationship of the Herxheimer reaction not only to the dosage of penicillin administered but also to the disappearance of T. pallidum from dark field positive lesions in the same group of patients. With 300 to 120,000 Oxford units of penicillin per kilogram of body weight, early lesions became dark field negative between nine and thirteen hours after the initial injections in all cases.[18] Six to ten hours after the injection was given febrile reactions occurred in one half of these patients. With 100 to 150 Oxford units of penicillin per kilogram of body weight, lesions became dark field negative after longer time intervals, which varied from eighteen to forty-eight hours after administration of the injection. In a low dosage range (10 to 80 units per kilogram of body weight), results of dark field examinations remained persistently positive for forty-eight hours. However, Herxheimer reactions occurred after the same time interval and in the same proportion as observed with larger doses. Only with minute doses of penicillin (1 to 5 units per kilogram of body weight) were febrile reactions not observed. Thus, Herxheimer reactions occurred with doses of penicillin as little as one tenth of the minimal amount required to render lesions dark field negative.

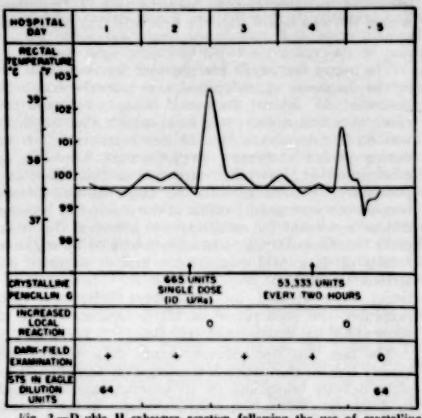

Fig. 2.—Double Herxheimer reaction following the use of crystalline penicillin G in a 62 year old white man. The diagnosis was secondary syphilis.

Double Herxheimer Reaction.—Eight patients, who had shown febrile reactions to small single doses (10 to 20 units per kilogram of body weight) of penicillin (table 3), again experienced febrile reactions when they were given either a therapeutic dose or a repeated small dose of penicillin twenty-four to seventy-two hours later. This double Herxheimer reaction is illustrated in figures 2 and 3. The temporal pattern and the height of the second febrile reactions were similar to those of the first. In these patients results of repeated dark field examinations remained positive for T. pallidum in the time intervals between the first and second doses.

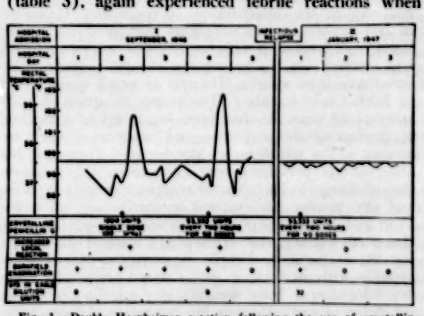

Fig. 3.—Double Herxheimer reaction following the use of crystalline penicillin G in a 19 year old Negro boy. The diagnosis was seropositive primary syphilis. The reaction followed the use of penicillin for the original infection. No febrile reaction occurred after the administration of the drug for infectious relapse.

This reduplication of the reaction was not observed after repeated large single doses of penicillin. Five

18. Tucker, H. A., and Robinson, R. C. V.: Disappearance Time of Treponema Pallidum from Lesions of Early Syphilis Following Administration of Crystalline Penicillin G., Bull. Johns Hopkins Hosp. 80: 169-173 (March) 1947.

patients, who had shown febrile reactions to large initial doses (20,000 to 120,000 units per kilogram of body weight) of penicillin (table 3), were given therapeutic doses (2,000 to 4,000 units per kilogram of body weight) of the drug twenty-four to seventy-two hours later. None of these patients showed a second febrile reaction. Results of dark field examinations in this group of patients became negative for T. pallidum within thirteen hours after the first injection was given.

COMMENT

The use of the febrile Herxheimer reaction as an aid in the diagnosis of undetected early syphilis has been described by several authors.[19] They have reported cases of unsuspected syphilis in which the diagnosis was made only after a Herxheimer reaction, occurring during penicillin therapy for gonorrhea, tonsillitis or other infection, had called attention to this diagnostic possibility. In some patients the diagnosis was missed because of the unusual location of the chancre or because it was concealed by inflammatory phimosis. In other cases the diagnosis was seemingly excluded by negative results of dark field examination and/or negative reactions to serologic tests for syphilis. When such patients were treated for concurrent infections with penicillin, the observation of febrile reactions was of some aid in the diagnosis of syphilis.

The fact that the reaction occurs only in approximately half of the patients treated with penicillin does place definite limitations on its practical use as an aid in diagnosis. When the reaction occurs in its characteristic temporal pattern, it may be of some presumptive diagnostic value. However, the absence of a febrile reaction does not exclude the presence of syphilitic infection.

In early syphilis the symptoms of the Herxheimer reaction are minor and incidental ones, which do not require the interruption of treatment. However, in late syphilis severe reactions attributed to the institution of treatment with penicillin have been reported, and methods for the prevention of such potential hazards have been sought. The use of small initial doses of 1,000 Oxford units (20 units per kilogram of body weight) of penicillin has been suggested as a method of decreasing the incidence and severity of such reactions in the treatment of late syphilis. However, the observations presented here concerning the relationship of dosage to Herxheimer reactions in early syphilis, and also similar observations in cardiovascular syphilis[20] and in neurosyphilis,[21] do not support the view that small initial dosage represents a method of preventing these reactions. Febrile responses occur in early syphilis with as little as 500 Oxford units (10 units per kilogram of body weight) of penicillin. Also, the repetition of small doses or the institution of therapeutic doses of penicillin after such an initial small dose is usually followed by a second febrile response. Thus, with small doses of penicillin one may obtain repeated Herxheimer reactions, but small dosage cannot prevent the reaction.

The mechanism of the Herxheimer reaction in early syphilis is not known. However, this reaction has been generally ascribed to the sudden destruction, presumably by lysis, of large numbers of spirochetes and the subsequent liberation of breakdown products of proteins or of an endotoxin. If this hypothesis were correct, then the frequency and severity of the phenomenon would vary directly with the total number of spirochetes destroyed. This number, in turn, would be a function of the dosage of the antispirochetal drug employed and of the total number of invading organisms originally present. However, the following observations presented in this study concerning these two variables are in disagreement with this hypothesis:

1. Over a wide range of dosage (10 to 120,000 units per kilogram of body weight) of penicillin there was tremendous variation in the number of spirochetes destroyed. Nevertheless, the incidence and severity of febrile reactions were remarkably constant.

(*a*) Febrile reactions repeatedly occurred in patients given small initial doses (10 to 80 units per kilogram of body weight) of penicillin, which, as judged by results of serial dark field examinations of superficial lesions, destroyed smaller numbers of spirochetes than were killed with large doses.

(*b*) The administration of large initial doses (20,000 to 120,000 units per kilogram of body weight) of penicillin did not increase the incidence or severity of Herxheimer reactions. Even with these large doses certain patients failed to show any reaction whatsoever, in spite of the fact that all detectable superficial spirochetes were destroyed within nine to thirteen hours after the injection was given, just as they were in patients who did have reactions.

2. Febrile reactions to the administration of penicillin were as frequent and as severe in seronegative primary syphilis as in secondary syphilis. This observation suggests that the reaction is not directly dependent on the total number of spirochetes originally present in the body, which may be presumed to increase from the date of infection until the height of florid secondary syphilis.

The observations presented here concerning the mechanism of the Herxheimer reaction suggest that in addition to the two factors already discussed (the number of invading spirochetes and the dosage of the antispirochetal drug), a third factor, namely, the reactivity of the host at the time of treatment, plays a dominant role in this phenomenon. At some time during the incubation period of syphilis the number of spirochetes present in the host increases to a quantity sufficient to produce a reaction. Therefore, a certain unknown minimal number of spirochetes is a first requisite. Secondly, a minimal amount of an antispirochetal drug (e.g., at least 10 to 20 units of penicillin per kilogram of body weight) is needed. Further increases in the number of spirochetes or in the dose of the drug above these threshold levels appear to play no further role in the mechanism of the reaction. Thus, this reaction, is an "all or none" type of phenomenon. When a threshold level of dosage is reached, the reaction occurs in about half of the patients. However, a third important set of unknown variables in different persons with syphilitic infections separate the reactors from the nonreactors. Further observations on the mechanism of this reaction are desirable.

SUMMARY AND CONCLUSIONS

Febrile Herxheimer reactions were observed in 41 per cent of 939 patients with early infectious syphilis treated with crystalline penicillin G. No race or sex

19. Leifer and Martin, 15b Ricchiuti, J. F.: Penicillin Therapy in Gonorrhea with Associated Undiagnosed Early Syphilis, U. S. Nav. M. Bull. **42**: 1031-1033 (Nov.) 1944. Bauer, F. K., and Ezell, C. F.: Herxheimer Syndrome Following Penicillin in Unsuspected Syphilis, Bull. U. S. Army M. Dept. **21**: 239-241 (Aug.) 1945. Cronin, E.: "Masked" Syphilis: Dangers of Penicillin Therapy, Lancet **2**: 84-85 (July 20) 1946.

20. Tucker, H. A., and Farmer, T. W.: Penicillin in Cardiovascular Syphilis: Early Reactions to Administration, Arch. Int. Med. **80**: 322-327 (Sept.) 1947.

21. Farmer, T. W., and Hoekenga, M.: The Jarisch-Herxheimer Reaction in Neurosyphilis Treated with Penicillin, unpublished data.

differences in the incidence of febrile reactions were noted.

Febrile reactions were observed with equal frequency and severity in seronegative primary, seropositive primary and secondary syphilis.

In a group of 56 patients with relapsing secondary syphilis treated with penicillin, the incidence of fever was 50 per cent with the first and 38 per cent with the second course treatment. Recurrent reactions were no more frequent in those whose first course of treatment was attended by a febrile reaction than in those who had had no fever the first time.

Within a wide range of penicillin dosage (10 to 120,000 units per kilogram of body weight) the incidence of febrile reactions remained relatively constant (40 to 56 per cent). With extremely small doses of penicillin (1 to 5 units per kilogram of body weight) febrile reactions were not observed.

The temporal pattern of the febrile reaction was rather uniform and was independent of the dosage over a wide range.

Febrile reactions occurred with single doses of penicillin as little as one tenth of the amount required to render syphilitic lesions dark field negative.

With repeated small doses of penicillin (10 to 20 units per kilogram of body weight) two febrile reactions were produced in the same patient. This double Herxheimer reaction was not observed after repeated large doses of penicillin.

The mechanism of the Herxheimer reaction from penicillin in early syphilis is not clear. It is suggested that the available evidence does not justify the hypothesis that the reaction is due solely to the sudden destruction of large numbers of spirochetes with the liberation of split proteins or endotoxins.

Further studies of the phenomenon are desirable.

THERAPY OF CHRONIC "ATROPHIC GASTRITIS" WITH EIGHT YEARS' GASTROSCOPIC CONTROL

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The anatomic entity known as chronic "atrophic gastritis" may be observed gastroscopically to improve or disappear from the stomachs of patients having pernicious anemia after liver therapy. Since the initial report of this observation by Jones, Benedict and Hampton[1] in 1935, several other reports[2] have appeared in the literature. In addition, gastroscopic changes in the atrophic gastric mucosa of patients without pernicious anemia have been observed by several investigators after specific types of therapy. Some of the substances used are dessicated hog's stomach ("ventriculin") by Schiff and Goodman,[3] liver and iron by Schindler, Kirsner and Palmer[4] and others,[5] thiamine by Bower[6] and others, and the separate components of the vitamin B complex by Shapiro and his associates.[7] Each of these studies was made on extremely small groups of patients and followed over relatively short periods of time. Some observers reported disappearance of atrophy with or without recurrences, while others have reported no changes.

Our studies began in 1938 with 60 patients. Excluding those on whom insufficient data were obtainable, we are here reporting the observations on 36 patients who received therapy and a control group of 16 patients who had no specific therapy or on whom therapy was started after a control period. The observations were both clinical and gastroscopic and extended over varying periods up to eight and one-half years. The chief differences between our study and those reported in the literature are as follows: (1) a much longer observation time, (2) more gastroscopic examinations and (3) the use of a control group and control periods, which were not carried out in most of the other studies. It was felt that in dealing with such a chronic disorder, longer periods of observation should have distinct advantages. The importance of controls and frequent examinations is obvious.

Our patients were all of the poorest economic class, indigents who had experienced a long period of unemployment and a longer period on the rolls of relief agencies during the years leading up to 1938. As indicated by dietary questionnaires, the food intake of these patients was considerably below the standards of normal nutritional requirements, both as to quantity and quality. Their undernutrition was further evidenced by plasma ascorbic acid levels below 1 mg. per hundred cubic centimeters in 95 per cent of the cases; low grade hypochromic anemia and varying degrees of loss of weight. However, on the basis of physical examination alone the entire picture might have been missed because of the sparseness of physical evidence of frank deficiency disease. It was observed by one of us[8] that there was a greater incidence of so-called atrophic gastritis in a series of 702 patients who underwent gastroscopy prior to 1941 than that reported by other workers in this field. For example, Schindler[9] found among 1,000 dyspeptic patients at the Billings Hospital in Chicago that 32.5 per cent of the chronic gastritis seen was of the atrophic type, while in our own series the incidence was 53.6 per cent.

It may be necessary to state here that while patients of the lowest economic level seem to have the highest incidence of atrophic gastric mucosa, it does not necessarily follow that persons of the highest economic level will escape such gastric changes. It should not be overlooked that many persons to whom adequate quantities and qualities of food are available have capricious appetites and eat only foods which appeal most to their tastes. Also it is probably true that there are some gastric atrophies which are not of dietary origin either directly or indirectly.

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THERAPY

Our patients with so-called atrophic gastritis were divided into five groups for purposes of therapy and one group for control (table 7). The first group (table 1) consisted of 10 patients who received injections of 1 cc. of vitamin B complex[10] intramuscularly each day for twelve injections. Such a course was repeated three to four times, and gastroscopy carried out at the end of each course. Larger doses were given in some cases when indicated for the desired effect. Gastroscopy was performed for months and up to seven years after cessation of therapy. Four of these patients underwent gastroscopy an average of twelve times in eight to nine years; 3 patients average nine examinations in five to seven years, and 3 others averaged seven examinations from seven to two years.

The second group (tables 2, 3 and 4) consisted of 18 patients who received injections of liver extract[11]. Ten of them received daily injections in courses similar to those of the vitamin B complex in group 1. Four patients received 3 cc. of liver injections once a week and 1 Gm. of ferrous sulfate per day orally. The 4 remaining patients in this group received weekly injections of liver extract and 20 to 30 minims (1.3 to 2 cc.) of dilute hydrochloric acid by mouth three times a day. The patients were observed from one to eight years and underwent gastroscopy from three to twelve times each.

In the group given vitamin B complex in 7 out of 10 cases atrophy disappeared; in 4 cases it returned to some degree. The remaining 3 cases showed improvement, 1 with regression.

In the group given liver extract in 12 out of 18 cases atrophy completely disappeared; in only 2 cases did it return. The addition of iron or dilute hydrochloric acid did not bring about improvement greater than daily administration of liver extract alone.

"Nicamin" (monoethanolamine nicotinate),[11] containing 50 mg. of nicotinic acid, was given in daily doses—intramuscularly to 4 patients—and observations were made from six months to seven years (table 5). Two cases showed disappearance and return of atrophy. One case of pronounced arteriosclerosis showed no changes.

Dilute hydrochloric acid alone was given to 4 patients.

TABLE 1.—*Changes in "Atrophic Gastritis" During and After Injections of Vitamin B Complex**

Patient	Case No.	Gastroscopies: First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	Tenth	Eleventh	Twelfth	Thirteenth	Fourteenth	Total Period
J.J.	5	12-16-37 3+	1-20-38 3+	11-3-38 3+	6-20-39 3+	10-16-39 3+	11-27-39 2+	1-29-40 2+	3-1-40 0	7-25-40 1+	9-25-44 2+					7 yr.
N.C.	24	7-11-39 3+	1-25-40 3+	3-11-40 3+	4-1-40 2+	4-14-40 2+	6-6-40 0	11-9-44 0	4-10-47 1+							8 yr.
J.K.	17	10-6-39 3+	10-16-39 3+	12-28-39 3+	1-29-40 3+	2-15-40 2+	1-29-40 3+	3-11-40 2+	5-2-40 0	7-15-40 0	3-5-41 0					1½ yr.
F.W.	38	3-11-40 3+	12-23-40 3+	3-10-41 3+	9-29-41 1+	1-26-42 0										2 yr.
P.W.	34	10-2-39 4+	2-1-40 4+	2-24-40 3+	3-11-40 3+	4-15-40 2+	5-2-40 1+									7 mo.
W.J.	18	11-16-39 3+	12-7-39 2+	1-8-40 0	2-29-40 2+	3-21-40 0	5-27-40 0	7-15-40 0	11-20-44 0							5 yr.
D.G.	11	1-29-40 4+	2-29-40 3+	3-21-40 2+	4-4-40 1+	6-20-40 1+	7-15-40 2+	8-22-40 1+	5-5-47 4+							7 yr.
V.H.	1	12-5-38 3+	7-25-39 3+	9-27-39 2+	12-11-39 1+	4-25-40 2+	7-11-40 1+	1-6-41 1+	9-25-44 1+	4-21-47 1+						8½ yr.
C.B.	12	3-17-38 3+	5-12-38 2+	6-21-38 2+	8-2-38 1+	10-13-38 1+	2-12-39 0	6-1-39 0	11-2-39 0	12-14-39 0	3-14-40 2+	4-29-40 1+	5-15-41 1+	10-30-44 1+	4-17-47 3+	9 yr.
E.W.	33	4-6-39 3+	8-1-39 3+	12-4-39 1+	1-22-40 2+	2-14-40 2+	3-7-40 1+	3-25-40 0	6-20-40 1+	9-12-40 1+	10-7-40 1+	1-9-41 1+	5-15-41 1+	7-28-41 0	4-14-47 1+	8 yr.

*Period between lines indicates the period of therapy. Extensive atrophy is indicated by 4+, moderate by 3+, mild by 2+ and minimal by 1+, and disappearance of atrophy by 0.

TABLE 2.—*Changes in "Atrophic Gastritis" During and After Daily Injection of Liver Extract**

Patient	Case No.	Gastroscopies: First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	Tenth	Eleventh	Twelfth	Total Period
A.C.	25	4-27-39 3+	2-8-40 2+	3-7-40 1+	6-3-40 0									14 mo.
M.P.	9	3-9-39 4+	10-16-39 3+	9-5-40 2+										18 mo.
T.F.	13	6-9-38 3+	12-18-39 3+	2-12-40 2+										20 mo.
N.B.	3	10-12-39 3+	1-15-40 4+	3-28-40 2+	5-2-40 0	5-20-40 0	6-11-40 0	10-7-40 0	11-13-44 0					5 yr.
R.E.	7	5-8-39 3+	10-23-39 0	3-7-40 2+	4-4-40 2+	4-25-40 1+	7-8-40 1+	9-22-40 0	10-25-43 1+	11-11-44 0				5 yr.
S.P.	16	1-16-39 3+	10-9-39 2+	2-5-40 0	3-25-40 0	5-27-40 0	7-22-40 0	9-16-40 0						18 mo.
A.T.	47	3-30-39 0	6-6-39 2+	1-11-40 1+	3-28-40 0									1 yr.
M.G.	21	11-3-38 4+	1-12-39 4+	4-13-39 4+	10-2-39 4+	3-7-40 3+	4-4-40 3+	5-2-40 2+	5-20-40 4+†	9-23-40 3+	12-2-40 3+	12-29-40 2+	4-25-44 1+	6½ yr.
I.B.	45	12-1-38 3+	10-16-39 2+	1-15-40 0	6-17-40 0									6 mo.
O.H.	55	1-6-38 2+	6-2-38 3+	8-2-38 2+	4-14-41 2+									3 yr.

*Period between lines indicates the period of therapy. Extensive atrophy is indicated by 4+, moderate by 3+, mild by 2+ and minimal by 1+, and disappearance of atrophy is indicated by 0.
†Loss of weight because of failure to eat.

10. The vitamin B complex was supplied by Lederle Laboratories, Inc.

11. The "nicamin" and liver extract were supplied by Abbott Laboratories, North Chicago, Ill. Liver extract contained 5 pernicious anemia units per cubic centimeter.

tients over a period of six months to three and one half years (table 6). No changes occurred in 3 of these patients, but atrophy disappeared after one year of therapy in the remaining patient. This may not be a spontaneous remission, since 2 control patients observed for one year each showed no improvement in atrophy.

SYMPTOMATIC RESULTS

Symptomatically there was a most dramatic improvement after the daily injection of liver extract, vitamin B complex and nicotinic acid. Improvement but less dramatic results occurred after administration of dilute hydrochloric acid. Beneficial effects were related to gastric changes. The constipation, general abdominal bloating, dizziness, etc., could very well be related to the bowel. Such symptoms are well known in vitamin B complex deficiencies. The nervousness, weakness, anorexia, etc., may be related to the nervous system or more general metabolic disturbances. The symptom complex seems definite enough and sufficiently different from that of pernicious anemia with gastric atrophy to warrant designation as a definite syndrome.

No Return of Atrophy.—In summary, the gastroscopic results of our studies were as follows: The daily injections of liver extract give the best and most permanent results. Some cases observed gastroscopically up to seven years with no further therapy, but improved diet, showed no return of gastric atrophy. One or more instances of complete disappearance of atrophy occurred in each therapeutic group. There was no spontaneous decrease of atrophy in any of the 16 control patients who either received no specific therapy or were on control periods up to twelve months. In a few cases atrophy disappeared almost completely and showed no further improvement or regression over a period of years.

TABLE 3.—*Changes in "Atrophic Gastritis" During and After Weekly Injection of Liver Extract Plus Oral Iron, Daily**

Patient	Case Number	Gastroscopies: First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	Tenth	Total Period
B.V.	35	5-29-39 4+	7-15-40 1+	9-9-40 1+	10-6-41 1+	1-10-44 1+	11-27-44 1+	3-20-47 1+	4-10-47 1+			8 yr.
J.M.	4	1-26-39 4+	2-3-39 4+	7-18-39 3+	3-21-40 1+	4-15-40 2+	5-2-40 2+	6-6-40 2+	7-8-40 0	7-22-42 0	10-23-44 3+	6 yr.
R.P.	8	7-25-39 3+	12-18-39 0	2-26-40 0	4-18-40 0							9 mo.
E.D.	6	1-12-40 3+	5-13-40 2+	6-17-40 1+	7-1-40 0	1-27-41 0	5-6-47 0					7 yr.

*Period between lines indicates the period of therapy. Extensive atrophy is indicated by 4+, moderate by 3+, mild by 2+ and minimal by 1+, and disappearance of atrophy by 0.

usually experienced by the end of the second week. The symptoms [12] complained of in order of frequency were epigastric pain, aching, fulness, tenderness, burning, cramping, bloating and belching shortly after meals and especially after heavy foods, constipation, nausea with occasional vomiting, anorexia, dizziness, generalized weakness often in attacks, loss of weight, loss of strength and energy, nervousness, tremor in the epigastrium, feeling of heat in the epigastrium. All these symptoms were alleviated either partially or completely. Occasionally there was some moderate return of symptoms, but none of the patients felt as ill as before therapy. After Pearl Harbor, practically all these patients became gainfully employed. More food and a greater variety of it was available. Most of them soon gained in weight and strength, and their improved symptomatic status continued through the remainder of the eight years' period of observation. These observations strongly suggest a dietary deficiency as the cause of gastric mucosal atrophy. It appears unlikely that a local inflammation of the gastric mucosa should cause the multiplicity and variety of symptoms described. It is more probable that the symptoms are caused by a generalized metabolic or nutritional deficiency syndrome of which gastric mucosal atrophy is only a part. The epigastric distress may be directly related to gastric changes. The constipation, general abdominal bloating, dizziness, etc., could very well be related to the bowel. Such symptoms are well known in vitamin B complex deficiencies. The nervousness, weakness, anorexia, etc., may be related to the nervous system or more general metabolic disturbances. The symptom complex seems definite enough and sufficiently different from that of pernicious anemia with gastric atrophy to warrant designation as a definite syndrome.

12. A table showing incidence of symptoms was compiled but was not submitted for publication.

TABLE 4.—*Changes During and After Liver Extract Weekly and Dilute Hydrochloric Acid Therapy Daily**

Patient	Case Number	Gastroscopies: First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	Tenth	Total Period
F.B.	45	12-1-38 4+	1-16-39 2+	5-15-39 2+								6 mo.
M.J.	19	10-6-38 3+	11-17-38 3+	2-25-39 2+	10-5-39 2+	7-11-40 4+	9-19-40 4+					2 yr.
A.G.	21	4-27-39 3+	7-27-39 3+	5-27-40 0								1 yr.
A.T.	48	3-30-39 0	6-6-39 2+	1-11-40 1+	3-18-40 0							1 yr.

*Period between lines indicates the period of therapy. Extensive atrophy is indicated by 4+, moderate by 3+, mild by 2+ and minimal by 1+, and disappearance of atrophy by 0.

Recurrences of Atrophy After Disappearance.—Our patients also showed some recurrences of atrophy. Of interest is the fact that of the 6 patients showing recurrences of atrophy, 4 were moderate alcoholic addicts (cases 12 and 33, table 1, and cases 7 and 4, tables 2 and 3 respectively). These patients continued to drink moderately during the entire period. Atrophic changes decreased and partially returned even during therapy, only to decrease again. This observation does not prove, however, that the changes were due to the irritation of the alcohol, in our opinion. There is the strong possibility that the atrophy might have been due to substitution of alcohol for food, in which case the recurrent atrophy would still be of dietary origin.

No Improvement of Atrophy after Therapy.—Only 4 of our patients failed to show improvement after therapy. Two had received dilute hydrochloric acid

only. The third was a woman, aged 65 (case 10, table 5), with pronounced generalized arteriosclerosis. She received extensive injections of liver extract, followed by vitamin B complex and then nicotinic acid over a period of one year without any improvement in the

TABLE 5.—*Changes in "Atrophic Gastritis" During and After Injections of Nicotinic Acid**

		Gastroscopies							
Patient	Case No.	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Total Period
E.E.	20	6-24-40 4+	10-11-40 4+	12-12-40 4+	1-16-40 3+	9-21-41 0	4-17-47 4+		7 yr.
V.R.	14	1-22-40 4+	4-18-40 4+	7-15-40 4+	9-26-40 3+	12-9-40 2+	8-4-41 0	10-23-44 2+	5 yr.
C.B.	46	10-28-40 3+	11-14-40 3+	3-6-41 1+					6 mo.
A.C.	10	12-23-37 4+	6-12-39 3+	10-23-39 4+	1-22-39 4+	4-15-40 3+			3 yr.

*Period between lines indicates the period of therapy. Extensive atrophy is indicated by 4+, moderate by 3+, mild by 2+ and minimal by 1+, and disappearance of atrophy by 0.

gastroscopic picture of atrophy. She had been seen in the clinic for two or three years before gastroscopy, and her dyspeptic symptoms had been explained on the basis of "abdominal arteriosclerosis." It appears that the atrophy in this case was due at least in part to the arteriosclerosis and diminished blood supply to the gastric tissues and was therefore little affected by any of

TABLE 6.—*Changes in "Atrophic Gastritis" During and After Dilute Hydrochloric Acid Therapy**

		Gastroscopies							
Patient	Case No.	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Total Period
A.S.	50	5-27-40 4+	11-25-40 4+						6 mo.
A.M.	37	11-10-38 4+	3-27-39 2+	11-10-39 4+	1-15-40 4+	2-26-40 0	9-26-40 0		2 yr.
E.B.	45	12-1-38 4+	1-16-39 2+	5-15-39 2+					17 mo.
W.P.	44	7-8-40 4+	11-14-40 4+	12-9-40 4+	1-9-41 4+	1-12-42 4+			3½ yr.

*Period between lines indicates the period of therapy. Extensive atrophy is indicated by 4+, moderate by 3+, mild by 2+ and minimal by 1+, and disappearance of atrophy by 0.

the therapy employed. The other patient was one who also had adrenal cortical insufficiency.

Gastric Mucosal Atrophy and Chronic Superficial Gastritis.—In several instances during the therapeutic period, chronic superficial gastritis was seen to be superimposed on the underlying picture of atrophy. With therapy the superficial gastritis would disappear leaving the more slowly healing atrophy (cases 12 and 33, table 1). This process has been seen to repeat itself in the same person in several instances. The point therefore arises that the simultaneous occurrence of chronic superficial changes and atrophic changes does not invariably indicate that chronic superficial gastritis has progressed to chronic atrophic gastritis. We believe that in many instances these findings represent chronic superficial gastritis, superimposed on an atrophic gastric mucosa of nutritional deficiency origin. The differentiation is important because the term "atrophic gastritis" implies a local inflammatory disease. Gastric mucosal atrophy seems to be in most instances a manifestation of a generalized deficiency state requiring an entirely different approach in therapeutic management.

OTHER INTERESTING FACTS IN THE EIGHT YEAR STUDY

One patient with an extensive atrophy of the gastric mucosa was observed to have pernicious anemia four years later. During five years in the clinic previously he had shown no evidence of anemia. In this case, atrophy of the gastric mucosa is known to have preceded pernicious anemia by at least a few years. With one exception, all the patients reported in this study survived the development of gastric cancer, in spite of their atrophic gastric mucosa for at least eight years. The 1 patient died in another hospital of gastric carcinoma seven years after the initial gastroscopic finding of mucosal atrophy. Gastric mucosal atrophy might well have been the predisposing factor to cancer in this case. More cases of this kind which will be found only by long term follow-up studies might eventually settle the question of the relationship between gastric mucosal atrophy and gastric cancer.

CONCLUSIONS

(1.) Further evidence of the therapeutic response of gastric mucosal atrophy to nutritional substances is presented. (2.) After nutritional therapy, prompt and dramatic relief of the entire symptom complex occurs; it may not return in seven years or more if a normal diet is followed. (3.) Atrophic gastric mucosa may regain and maintain normal appearance for seven years or more when followed by a normal diet.

(4.) There is a high incidence of gastric mucosal atrophy among economically poor and malnourished patients. (5.) Gastric mucosal atrophy in patients without pernicious anemia seems to be a part of a generalized "nutritional deficiency syndrome" rather than a local inflammatory disease and warrants specific designation.

(6.) Gastric mucosal atrophy may precede pernicious anemia and gastric carcinoma by several years.

TABLE 7.—*"Atrophic Gastritis" During Control Period Without Therapy**

	Control Period Before Therapy											Gastroscopic Examinations Control Period, No Therapy			
Subject	F.W.	O.H.	J.K.	N.C.	V.R.	C.V.	T.F.	V.H.	P.W.	J.J.	E.E.	H.N.	G.G.	M.D.	A.A.
Case	38	55	17	24	14	46	15	1	34	5	20	48	62	63	61
	3-14-40 3+	1-6-38 2+	10-6-39 3+	7-11-39 3+	1-22-40 4+	10-28-40 3+	6-9-38 3+	12-5-38 3+	10-3-39 4+	12-16-37 3+	6-24-40 4+	11-27-39 2+	10-24-40 2+	2-2-42 3+	6-5-39 2+
	12-23-40 3+	6-2-38 2+	10-16-39 3+	1-25-40 3+	4-18-40 4+	11-14-40 3+	12-18-39 3+	7-25-39 3+	2-1-40 4+	1-20-38 3+	10-3-40 4+	12-7-39 2+	11-11-40 2+	3-12-42 3+	12-18-39 2+
	3-10-41 3+		12-28-39 3+	3-11-40 3+	7-15-40 4+						1-15-40 3+				6-20-40 3+
Total Period	1 yr.	6 mo.	3 mo.	9 mo.	7 mo.	1 mo.	18 mo.	7 mo.	4 mo.	1½ mo.	4 mo.	3 mo.	2 wk.	1 mo.	1 mo.	1 yr.

*Extensive atrophy is indicated by 4+, moderate by 3+, mild by 2+ and minimal by 1+.

DISTINCTIONS BETWEEN GASTRIC SARCOMA AND CARCINOMA

With Special Reference to the Infiltrating Types of Sarcoma

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This article is based on a series of 20 cases of advanced sarcoma of the stomach confirmed either by operation or autopsy. We are concerned with the various signs, symptoms and laboratory findings which could aid in making a preoperative diagnosis of gastric sarcoma. These features are compared and contrasted with similar features found in advanced carcinoma of the stomach. We believe that sarcoma of the stomach could be diagnosed more often. In this series of sarcoma 11 cases were lymphosarcoma, 3 were of the spindle cell variety and 6 were round or mixed cell alveolar sarcomas. In 11 of the 20 cases features were present to warrant a supposition that sarcoma rather than carcinoma existed.

Pathologic distinctions of gastric sarcoma based on tissue derivation, while scientifically valuable, can be made only by microscopic examination. It is generally accepted that the cytologic and embryologic variations of sarcoma present no distinctions clinically; indeed, it probably always will be impossible to make a diagnosis of gastric sarcoma with qualification as to its cellular architecture.

Ewing's[1] estimate that sarcoma comprises 1 per cent of malignant tumors of the stomach is widely cited. More recently, Marshall and Aronoff[2] reported an incidence of 3.2 per cent in 464 patients operated on for gastric tumors at the Lahey Clinic. In 1944, at the Mayo Clinic, of 298 malignant lesions of the stomach, 3.3 per cent were sarcoma.[3] Phillips[4] reported that in persons under 30 years of age sarcoma comprised about 6.5 per cent of malignant gastric lesions. Thus it appears that sarcoma of the stomach is encountered more frequently than is generally assumed.

Ewing's[1] classification of gastric sarcoma is widely employed: (1) spindle cell myosarcoma; (2) lymphosarcoma, and (3) miscellaneous round cell or mixed cell alveolar sarcoma. Of these, lymphosarcoma is the type most frequently seen and comprises about 60 to 65 per cent of sarcomas encountered in the stomach.[5] It arises from the lymphoid tissue in the submucosa and usually infiltrates widely along the stomach wall into the muscularis and may penetrate the serosa causing perforation. This also holds true for some types of sarcoma in the miscellaneous group. The spindle cell myosarcomas are usually solid tumors, arising from the curvatures, and may protrude into the stomach or extragastrically.[6] They usually occur as circumscribed masses with well limited boundaries.

Ulceration usually occurs rather late in the course of gastric sarcoma and is caused either by vascular strangulation or pressure atrophy of the mucosa due to tumor formation in the submucosa. Usually the tumor spares the orifices; therefore dysphagia and pyloric obstruction are rare as compared to carcinoma. In reviewing the location of 100 cases of sarcoma of the stomach, D'Aunoy and Zoeller[7] listed their positions as follows: greater curvature, 17; pyloric region, 16; lesser curvature, 16; posterior wall, 12; diffuse infiltration, 11; anterior and posterior wall, 11, and anterior wall, 6. The remaining were situated on either the anterior or posterior wall and one of the curvatures, and only one was situated in the fundus.

A modification of Schlesinger's[8] clinical classification of gastric sarcoma is offered: (1) the exogastric, arising in the outer coats (or courses to the outer coats) but little involving the organ intragastrically; (2) intragastric, projecting in the lumen as an isolated growth, and (3) infiltrative type, which involves the stomach wall profusely and which may or may not project intragastrically.

DIFFERENTIATION OF GASTRIC SARCOMA FROM CARCINOMA

Age—The average age for persons with gastric sarcoma reported by D'Aunoy and Zoeller[7] in 135 cases was 36.7 years. Balfour and McCann[9] reported an average age of 43 years. In our series it was 38.5 years. These contrast with the average age of persons with carcinoma of the stomach, who are about ten to fifteen years older. This, however, should not be given too much significance because the age of our patients ranged from 18 to 78 years. Relatively, however, the younger the patient with malignant disease of the stomach, the greater is the probability of sarcoma.

Sex—Bockus[10] stated that sarcoma is only slightly more prevalent in the male. In the 135 cases reviewed by D'Aunoy and Zoeller[7] 73 of the patients were male and 43 female and in the remainder there was no information as to sex. Askey[11] and others in reviewing 335 cases reported 70 per cent occurring in males. In our series 75 per cent of the patients were male. The incidence of carcinoma in the sexes does not differ materially from that of sarcoma.

Duration of Symptoms—In sarcoma of the stomach symptoms may be present from two months to several years. In inoperable cases, the average duration of symptoms is thirty-seven months.[12] In our cases it was twenty-nine months. In carcinoma the average duration of symptoms is eight to twelve months. In sarcoma there is no relationship with previous peptic ulcer, while about 5 to 10 per cent of prepyloric gastric ulcers became carcinomatous.

Pain—Pain is the most common symptom; it occurred in 80 per cent of our cases. It is localized in the left upper quadrant, or tends to the left, although it may be epigastric completely. The pain is often more severe than that seen in carcinoma.[6] In about 50 per cent of the cases the pain simulates peptic ulcer,[13] but

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Read in symposium on Gastritis and Gastric Neoplasms before the meeting of the Section of Gastro-interology and Proctology at the Ninety-sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 12, 1947.

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13. Rafsky, H. A.; Katz, H., and Krieger, C. I.: Varied Clinical Manifestations of Lymphosarcoma of the Stomach, Gastroenterology 3:297-305 (Oct.) 1944.

this is not significant as it is often seen in carcinoma. The distinction, however, between relief of pain in ulcer and the two malignant diseases of the stomach is that in the latter there is progressive loss of weight.[13] In an analysis of 444 patients with gastric carcinoma, pain was present in 92.8 per cent.[14] Thus, pain is the most common symptom in both sarcoma and carcinoma. In a general way, it seemed to us that pain tended to be more severe in sarcoma, although there were 4 cases in which pain was absent.

Weakness, Cachexia and Anemia—Weakness, Cachexia and Anemia are generally grouped together in the literature, which makes it rather confusing on each of these points. Bockus[16] stated that anemia, loss of weight and strength and other constitutional symptoms occur with about the same frequency as in carcinoma. Rafsky and his associates[13] stated that they were usually absent in lymphosarcoma of the stomach. Madding[15] in reviewing 67 cases of sarcoma states that some patients complained of loss of weight, weakness and anorexia and that anemia (microcytic, hypochromic) was present in most cases but was not as great as in carcinoma. Drane[16] stressed the well preserved nutrition in cases of gastric sarcoma. In our opinion the symptoms of weakness, loss of weight, cachexia and anemia should not be grouped because individually they have varying degrees of differential diagnostic value. One is often struck by the surprising well-being of a patient with advanced sarcoma of the stomach. In our group of 20 patients, 12 (60 per cent) were employed at the time of examination. The remaining 8 patients complained of definite weakness. In roughly the same stage of carcinoma of 100 patients, weakness was present in 94 per cent. The same differential occurs concerning loss of weight. In carcinoma of the stomach, loss of weight is progressive and usually severe. Slight and short weight increases may occur, but a continuing decline soon supervenes. In sarcoma, the loss of weight was pronounced in only 7 of our patients. Eleven had lost a negligible few pounds and 2 had no definite loss of weight.

That the nutty brown color so characteristic of gastric carcinoma does not occur in sarcoma is a clinical point of interest. The skin is pallid and its appearance is that of a simple anemia. Very occasionally one sees a slight lemon tint as noted sometimes in leukemia.

There are no worth while points to present in the type or degree of anemia between the two diseases. The anemia may be slightly less in sarcoma. In 444 cases of carcinoma of the stomach, jaundice was present in 23.2 per cent.[14] It was absent in all our cases and we have seen no mention of its occurrence in sarcoma in the literature.

Vomiting and Hematemesis—Vomiting occurs in 8 to 10 per cent of gastric sarcoma,[17] and in 16 per cent of carcinoma.[14] Hematemesis is encountered in 15 to 20 per cent of sarcoma and about 10 per cent in carcinoma. It is important to remember that in sarcoma vomiting and hematemesis occur late probably because pyloric obstruction is less frequent than in carcinoma and the mucosa is secondarily involved in sarcoma. Bleeding in sarcoma is often severe and may be terminal.

Palpable Tumor—It is reported that a mass may be palpated in 30 to 50 per cent of gastric sarcoma.[18] In carcinoma this percentage is 80 per cent after the third month of symptoms. This difference is due to the fact that the largest percentage of sarcoma is infiltrative in character and thus may not form a definite, easily felt mass. Therefore the sarcoma may be of large extent and yet not be palpable. A sense of deep, diffuse resistance may be encountered rather than a localized hard mass and may be mistaken for a tumor of the pancreas, colon or kidney. In our 20 cases a tumor was palpable in 10. If the roentgenogram shows an extensive involvement of the stomach and no tumor is palpable, or only a doughy mass is observed, sarcoma should be suspected.

An enlarged spleen is palpable in 10 per cent of gastric sarcomas.[16] In our series the lower pole of the spleen was palpated in 3 (15 per cent). Palpable spleens are rare in carcinoma.

Virchow's gland, sometimes palpable in gastric carcinoma, is not observed in sarcoma. Visible gastric peristalsis, characteristic of pyloric obstruction, was not observed in our series.

Gastric Analysis—It is reported that 85 per cent of gastric carcinoma shows an absent or low free acidity.[15] Madding and Walters[5] stated that in lymphosarcoma of the stomach there is achlorhydria in the largest number of cases and that normal acid values are found in but 20 per cent. In our series 8 had acid values which were normal or above normal and 12 had decidedly lowered or absent free hydrochloric acid. Of these 12 patients showed no free hydrochloric acid but did have some combined hydrochloric acid (not total acid). Five were achylic. Therefore, there were 15 of 20 patients (75 per cent) who had hydrochloric acid (free or combined) in the gastric juice. This is distinctly higher than that observed in gastric carcinoma.

Blood in gastric contents and stools is encountered in about 65 per cent of carcinoma of the stomach.[14] All observers believe that the percentage is much lower for sarcoma. This is due to the fact that ulceration occurs much later in sarcoma and may be absent throughout the course of the disease. In our group of cases, blood was encountered in 4 instances. Death from exsanguination, however, is more frequent in sarcoma.

Gastroscopy—Schindler[19] stated that the infiltrative type of lymphosarcoma presents characteristic gastroscopic findings which cannot be mistaken for any other picture. This statement has not been accepted generally. Giere[20] reported a case of lymphosarcoma diagnosed gastroscopically one month after the roentgenogram had failed to disclose any abnormality. In solid tumors, the endoscope may disclose a solitary tumor with a sessile base, the rest of the mucosa appearing normal. (If the tumor is pedunculated, it probably is benign). In the infiltrative type of sarcoma, the gastric rugae are swollen and edematous. Later, ulcers and hemorrhages may be noted. The picture is not as characteristic as in carcinoma. Gastroscopy was performed in 16 of our cases. In 10 of these cases the diagnoses were: benign tumor 4, gastritis 2, Hodgkin's disease 2, leukemic infiltration 1 and tuberculosis 1. In the remaining 6 cases sarcoma was strongly suggested, all of which were instances of lymphosarcoma. The method should be employed, and it is of

14. Abraham, R. H., and Hinton, J. W.: Carcinoma of the Stomach, Surg., Gynec. & Obst. 71:135-141 (Aug.) 1940.
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194

especial value when its presumptive diagnosis of sarcoma agrees with that of the roentgen examination.

Roentgenographic Findings—The roentgen examination, properly conducted, is the most reliable method for diagnosis available. Rugal patterns should be studied with small quantities of barium. There should be adequate manipulation and palpation at roentgenoscopy. The fluoroscope is valuable especially in noting the solitary growths or masses projecting into the stomach, presence or absence of peristalsis and stiffening of the gastric walls. The statement that a positive diagnosis of sarcoma cannot be made by roentgen rays[21] or by any method short of exploration and biopsy[10] constantly runs through the literature. Rafsky and his associates[13] reported a definite roentgen diagnosis in 33 per cent of their series of lymphosarcoma. In our own series 11 of the 20 cases (55 per cent) were presumptively diagnosed as sarcoma. This percentage compares with a positive roentgen diagnosis of 90 per cent in carcinoma of the stomach.[14] There are points of difference in the roentgen findings of these two malignant diseases of the stomach.

Gastric deformities to be observed in sarcoma include the following: (1) a rounded, well defined endogastric mass, bearing a demonstrable ulcerative niche[22]; (2) a tumor arising on the greater curvature, even when it has the typical saucer shape of carcinoma; (3) giant rugae; (4) diffuse decrease in the size of the stomach; (5) absent or few "thumb indentations" characteristic of carcinoma, with the irregularity in gastric outline consisting of shallow serrations involving the stomach to considerable extent; (6) in localized sarcoma, a shadow may occur which is suggestive of benign tumor; at fluoroscopy it is not movable and usually is well rounded; in benign tumor the shadow is liable to be pedunculated, movable and irregular in outline; masses may be seen in carcinoma between the curvatures; when present in sarcoma, it is usually late in the disease, and while the tumor may be of large size (especially leiomyosarcoma) there is usually a small fleck of barium somewhere in the mass; most cases of sarcoma may never show a definite well defined tumor mass; (7) peristaltic waves are dependent on the amount of infiltration of the gastric wall; if intramural infiltration is extensive, peristalsis will be absent; however, in sarcoma, peristalsis, sluggish or irregular, is usually preserved later than in carcinoma. In our series, as already stated, a presumptive diagnosis of sarcoma rather than carcinoma was made in 55 per cent. A notable error is that shown in figure 1 (a case of Dr. Adolph Abraham).

Fig. 1.—Carcinoma diagnosed as sarcoma because of diffuse tumor formation and some shallow serrations of curvatures. There was no obstruction. Pathologic diagnosis was colloid carcinoma. On reexamination of films after operation it was noted that the growth is intragastric, the left half of the stomach appears normal and the defect on the greater curvature is more suggestive of carcinoma.

Another unusual case of hypertrophic gastritis that closely simulated the roentgen picture of malignant growth is illustrated by figure 2 (case of Dr. Harry Barowsky).

Fig. 2.—Deformity due to giant hypertrophic gastritis.

REPORTS OF CASES

The following 4 cases illustrate various features of gastric sarcoma.

CASE 1.—F. S., (a patient of Dr. Charles Friels, Jersey City), a farmer, 35 years of age, had been in good health until eleven months before being examined by one of us (A.B.). His illness began with anorexia, which became progressively worse. Three months later he began to complain of pain in the upper left part of the abdomen and vomited occasionally. There was a weight loss of 12 pounds (5.4 Kg.) over this period. Physical examination revealed no significant abnormality. No abdominal mass was palpable. Several test meals revealed normal values in the gastric contents, and in some a hyperchlorhydria existed. There was a mild degree of hypochromic anemia. Roentgen examination disclosed an isolated mass in the prepyloric region with no generalized involvement of the stomach. There was about 10 per cent gastric retention in six hours. Gastroscopically, a mass with a sessile base was seen and a few punctate hemorrhages were scattered in the mucosa. Because of the wide base by which the

21. D'Aunoy and Zoeller,[7] Madding.[12]
22. Carter, R. A. and Laing, D. R.: Non-Carcinomatous Tumors of the Stomach, Radiology 28:301-314 (March) 1937.

tumor was attached, a tentative diagnosis of solitary gastric sarcoma was made. At operation (subtotal gastrectomy) the tumor was removed and the pathologic diagnosis was spindle cell sarcoma. The patient died twenty-two months later from metastatic sarcomatous masses in the lungs, abdomen and subcutaneous tissue.

Comment—This case illustrates pronounced anorexia, slight loss of weight, absence of abdominal mass and normal gastric acidity. Roentgenograms revealed an immovable intragastric mass.

Case 2.—L. M., a young man of 18 years weighing 181 pounds (82.1 Kg.) complained of anorexia of four months' duration. "To get enough food" he had to resort to fluids and semisolid foods. He had lost 5 pounds (2.3 Kg.) over this period. There were no other complaints, he attended school regularly and engaged in athletics. Because his mother thought he looked pale, he was treated for moderate anemia. When first seen he presented slight nonpainful resistance in the epigastrium and mild hypochromic anemia; his gastric contents had a normal acidity. His stomach was extensively involved with infiltration of the walls and a diagnosis of gastric sarcoma was made. At operation an extensive partial gastrectomy was performed; the tissue diagnosis was lymphosarcoma. He died on the fourth postoperative day of an abdominal hemorrhage.

Fig. 3.—The stomach shows a generalized infiltrative process in the wall with diffuse decrease in size and irregular serrations on the curvatures. There is no obstruction. Lymphosarcoma.

Comment—This case illustrates the occurrence of lymphorsarcoma in youth, slight loss of weight, absence of constitutional symptoms and presence of normal gastric acidity.

Case 3.—W. R., (a patient of Dr. Pettit, Ridgewood, N. J.), a banker 68 years of age, had been troubled for ten years with a squamous cell carcinoma of the face. He had had a number of excisions, roentgen and radium treatments and when first seen had a large inflammatory area over the left ear. The upper third of the left external auricle was sloughed away, exposing the cartilage. During the preceding year he had lost considerable weight (14 pounds [6.4 Kg.]) and a mild degree of weakness had developed, although he was able to work. There were no gastric symptoms until six weeks before examination, when he became slightly nauseated and had diarrhea, both of which persisted. On examination, there was a soft diffuse mass (stomach) palpable in the epigastrium and extending to the right. The spleen was palpable and the liver edge firm and rounded. The red blood cells were 4,100,000, and there was 11 Gm. of hemoglobin per hundred cubic centimeters. The

Fig. 4.—Diffuse infiltration in the distal half of both curvatures with narrowing of the gastric lumen. Lymphosarcoma.

white blood cells were 9,100, with 74 per cent polymorphonuclear cells. An Ewald test meal revealed no free hydrochloric acid. Total hydrochloric acid was 25 degrees and total acidity

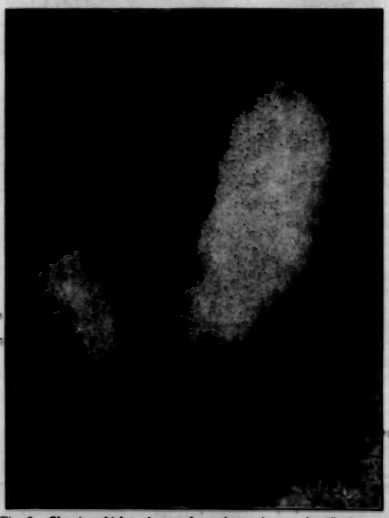

Fig. 5.—Showing thickened mass formation and general stiffening of the stomach in a case of leiomyosarcoma. The tumorous formation is noted about two thirds down the stomach. Irregularity along the lesser and greater curvatures indicates the general involvement of the stomach walls.

31 degrees. Roentgen examination revealed a generalized infiltration throughout the stomach with no apparent masses or obstruction. There was a mild degree of cardiospasm. A diagnosis of lymphosarcoma was made. At operation almost a

complete gastrectomy was performed; the stomach was diffusely infiltrated by the sarcomatous process and there was chronic adenitis of the omental lymphatic nodes. The patient died eight weeks postoperatively of acute heart failure, after he had seemed to be slowly improving.

Comment—This case is interesting because of the coincidental squamous cell carcinoma, short history of gastric symptoms, small loss of weight and palpable spleen. Hydrochloric acid was present in the gastric contents.

CASE 4.—A. J. (a patient of Dr. Emil J. Knips, Plandome, L. I.), a woman aged 49, mother of seven children, had a carcinoma removed from her breast ten years previously. Two years before being seen she began complaining of "nervousness" and pain in the region of the stomach. This pain became progressively worse for ten months. On physical examination a generalized doughy tumor was palpated in the upper part of the abdomen. Because of the character of the roentgenograms and a 4 plus Wassermann reaction, a diagnosis of gastric syphilis was made three months previously, and she had been placed on antisyphilitic therapy without benefit. She had lost only a few pounds in weight, was not anemic, had a fair appetite and consumed ample foods of all types, which, she said, did not increase her stomach distress or pain. She had vomited only twice, both times in the week before being seen by one of us (A. B.). Physical examination revealed the tumor described. An Ewald test meal showed hyperchlorhydria. The stools were negative for blood in several examinations. Roentgenograms showed a generalized stiffening of the stomach walls with absent peristalsis and with a mass in the pyloric region. The gastroscopic diagnosis was lymphosarcoma. The portion of the stomach with the tumor mass was removed. The pathologic report was leiomyosarcoma. The operation was followed by roentgen therapy over the stomach region. She died three months after the operation in the New York Hospital from a massive gastric hemorrhage.

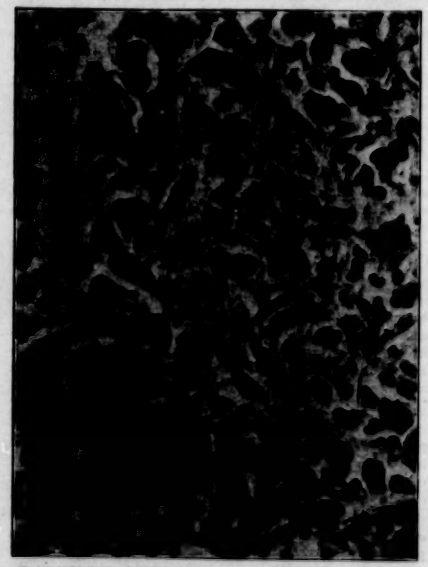

Fig. 4.—High power photomicrograph of tissue of the stomach, showing cells of various shapes and sizes with extremely large cells containing large nuclei and nucleoli predominating. In places these cells are spindle shaped and show characteristic tiny fibrils. Mitotic figures are noted throughout. Leiomyosarcoma.

Comment.—This case, which was originally diagnosed as gastric syphilis, illustrates but slight loss of weight with fair appetite. No anemia was present. There was hyperchlorhydria, and death was due to massive hemorrhage. This patient also had a carcinoma of the breast ten years before.

GENERAL COMMENT AND CONCLUSIONS

It is important in considering tumors of the stomach to realize that about 85 per cent are carcinoma. Rigler and Ericksen[23] stated that 11 per cent are benign, as noted earlier in this paper, slightly over 3 per cent are sarcomas. Even this figure of 85 per cent is high when one includes syphilis, tuberculosis, Hodgkin's disease, etc. If the possibility that a gastric malignant growth is not carcinomatous is continually entertained, the first and most important step toward the accurate presumptive diagnosis of gastric sarcoma is achieved. A careful evaluation of the various symptoms, signs and laboratory findings will, in increasing numbers, lead to a higher percentage of correct preoperative diagnoses. From the present group of cases and the literature on malignant disease of the stomach, we can draw the conclusions summarized in tables 1 and 2.

TABLE 1.—*Clinical Symptoms (in Percentages)*

	Sarcoma	Carcinoma
Age (years)	38.5	53
Sex, male	75	70
Duration of symptoms (months)	29	8-12
Previous history of peptic ulcer	0	5-10
Pain	80	92.8
Weakness (definite)	40	94
Weight loss (pronounced)	35	98
Cachexia	0	92
Jaundice	0	23.2

TABLE 2.—*Physical, Laboratory, Gastroscopic and Roentgen Findings (in Percentages)*

	Sarcoma	Carcinoma
Palpable tumors	50	80
Firm tumors	30	85
Soft (doughy) tumors	70	15
Palpable spleen	15	0
HCl, normal, increased	40	15
HCl, absent, low (combined)	60	85
Blood in gastric contents and stools	20	65
Suggestive gastroscopic diagnosis	37	75
Suggestive roentgen findings	55	90

In favor of a dignosis of gastric sarcoma as compared to carcinoma in an average way, the following points are noted:

1. Average age for sarcoma is 38.5 years; in carcinoma it is fifteen years older.
2. Because of slowness of the growth, sarcoma may extend twice or even three times longer than carcinoma.
3. There is no relationship with peptic ulcer in sarcoma.
4. Weakness in cases of sarcoma is less than half that of carcinoma.
5. Loss of weight is about one third that noted in carcinoma. In sarcoma there may be only slight anemia or none. In carcinoma it is more definite.
6. No jaundice is present in sarcoma; in carcinoma it occurs in 23.2 per cent.
7. Palpable tumor in sarcoma is a little more than half as common as in carcinoma. The sarcoma masses are vague and doughy in consistency, whereas in carcinoma, generally, the mass is easily felt and firm to hard in character. Visible peristalsis is not noted in sarcoma.
8. The spleen is enlarged in 15 per cent of the cases of sarcoma and not present in carcinoma.
9. Virchow's gland is not observed in sarcoma.
10. Hydrochloric acid of the free and combined types was present in 75 per cent of sarcoma; this figure is much higher than that found in carcinoma.
11. Blood in gastric contents and stools is observed in one third of the cases as compared to carcinoma.

23. Rigler, L. G., and Ericksen, L. G.: Benign Tumors of the Stomach, Radiology 30:6-15 (Jan.) 1938.

12. The gastroscope is less valuable in diagnosing sarcoma than carcinoma.
13. The roentgenograms are valuable in both conditions, although less so in sarcoma than in carcinoma.
14. Roentgen evidence suggestive of sarcoma is present in 55 per cent of the cases.

Recognizing that various combinations of findings are different in different cases, we would suggest a working formula as follows: (1) roentgen; (2) clinical findings and gastroscopy; and (3) laboratory. If the roentgenograms are definitely suggestive of sarcoma we would make a diagnosis. If the roentgenograms are not characteristic of carcinoma or sarcoma, we would give increasing importance to the features listed under (2) and (3), and if enough suggestive findings are met with we would make a presumptive diagnosis of sarcoma. One must keep in mind that in some cases of gastric sarcoma diagnosis is not possible even at operation without a microscopic examination of tissue.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. BERRY AND COLE AND DRS. BASSLER AND PETERS

DR. HYMAN I. GOLDSTEIN, Camden, N. J.: In 1920 and 1921 I studied the available literature of the world in preparation for papers on lymphosarcoma of the appendix. At that time I collected about 650 cases of primary sarcoma of the gastrointestinal tract, liver, pancreas and gallbladder. There were about 270 cases of primary sarcoma of the stomach, 18 of the appendix, about 150 of the intestines, 36 of the esophagus, 65 of the tongue, 16 of the gallbladder, 59 of the liver and 19 of the pancreas. Obstructive symptoms, occurring late in the course of the disease, are not uncommon in young patients. Symptoms may be absent for some time or only slight. Gastric lesions may become large and extensive before severe loss of weight and obstruction occur. Taylor (1939), Madding (1939), Collins and Carmody (1937) and others recently reported interesting cases of gastric sarcoma, as did Johnson, Lee and others, who stated, "Lymphosarcoma of the stomach is not a rare neoplasm." Their patient was a man aged 23 years. Dr. George Dock reported a case of "Sarcoma of the Stomach" while at Ann Arbor. The man was 55 years old. A successful gastrectomy was performed (1900), although he had the tumor for nearly two and one-half or three years. This patient lived until 1919. He died from pneumonia and had had no gastrointestinal symptoms for nearly twenty years! Halle's (1780-1781) case in a young woman with "Induration skirrheuse des membranes de l'estomac" was probably a gastric sarcoma. Since Mathis, in 1602, and Daniel Schwabe, in July 1635, performed sucessful gastrotomies, and Daniel Karl Theodor Merrem (1790-1859) of Giessen successfully resected the stomach in a dog (in 1810), we have made great progress in gastrointestinal surgery. We have overlooked the successful extensive resection of the intestines in a 13 year old boy by John Nedham (reported in 1756) and the first pylorectomy for cancer of the stomach, by Jules Pean (1830-1898) in 1879, before T. Billroth (1881). The speaker's report of about 28 or 30 five year survivals out of about 400 cases of gastric malignant growths is not encouraging. Perhaps early gastroscopy and earlier surgical intervention would save many more patients.

DR. HENRY A. RAFSKY, New York: I was interested in Dr. Berry's paper because I found that patients with atrophic gastritis improve when their nutritional status has improved. Dr. Bassler's paper is timely. Articles on these subjects should be encouraged because these so-called rare lesions, when we focus attention on them, are not as uncommon in an active ward service as we think they are. Lymphosarcoma of the stomach is the commonest type encountered. This lesion often mimics peptic ulcer in its onset and in its clinical course. At times we found hyperchlorhydria, but what we did not find until late in the disease was occult blood in the stool or in the gastric analysis. The clinical characteristics of carcinoma of the stomach, weight loss, anemia and cachexia, were not usually present in our series. The reason that carcinoma of the stomach can be detected earlier than lymphosarcoma lies in the difference in the pathologic changes of the two lesions. Gastric lymphosarcoma often arises extragastrically and invades the stomach from a lymph node or starts within the lymphoid tissue of the submucosa. It may become a large tumor involving and surrounding the stomach, and may exist without causing any symptoms, or may form an infiltrating process of the submucosa, producing a picture of severe gastritis or giant rugae. In a suspicious case sarcoma should be suspected, especially if the characteristic symptoms associated with carcinoma are not present.

DR. RUDOLF SCHINDLER, Los Angeles: We must no longer treat gastric carcinoma as one single disease entity. At least two forms must be differentiated: the sharply limited ones, types I and II, and the infiltrative forms, types III and IV. The limited forms are curable; the infiltrative forms are, with rare exceptions, incurable. The limited carcinomas must be removed even if they involve the whole stomach. To attack the infiltrative forms, except if they are small, is not practical. These patients have almost no chance of being cured, except perhaps by total gastrectomy. This consideration is especially important in the management of benign gastric ulcer. The differential diagnosis never lies between benign ulcer and limited carcinoma but only between benign ulcer and infiltrative carcinoma. Benign ulcer can well be treated medically; the resection has a definite mortality. Let us assume that the operative mortality of benign ulcer is only 3 per cent, and let us see what happens if we resect 100 stomachs which contain a doubtful ulcer. We will then kill, unnecessarily, 3 persons, if the ulcers are benign, in order to accomplish what, if they are all malignant? Practically nothing. Let us better concentrate on surgery for small-sized, beginning gastric carcinomas, which the surgeon may not be able to palpate but which may be diagnosed by roentgen examination and gastroscopy. If we follow our cases of pernicious anemia and atrophic gastritis, as Dr. Berry has, we will have a higher percentage of cures by discovering small symptomless carcinomas.

DR. SAMUEL FRIEDMAN, New York: A large number of patients suffering from cancer consult their physicians when it is too late. Physicians do not always make a diagnosis early enough for the surgeon to do a successful operation. How can we relieve the unnecessary suffering and reduce the death rate from cancer? Years ago I realized that we must feel equally responsible to our patients to relieve them as to cure them. We must caution patients of the seriousness of the delayed diagnosis. We must not be caught unawares in the diagnosis of serious diseases. For the past fourteen years I have been inviting my patients, four or five times annually, to my home to listen to lay lectures on the early symptoms of cancer and to lectures on many other serious ailments. These lectures, given by physicians and surgeons, and by myself, were usually attended by between 300 and 400 patients. Motion pictures of abdominal surgery, roentgenograms of tuberculous lungs and sound motion pictures on the heart in health and disease were shown. It is the sacred duty of physicians to reduce the suffering and mortality rate by teaching patients in groups, in the manner suggested. Judging from personal experience, I believe that half of those who die from carcinoma could probably live, and in comfort, if all physicians earnestly followed this suggestion.

Clinical Notes, Suggestions and New Instruments

STOMATITIS DUE TO STREPTOMYCIN

Report of Three Cases

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and
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Since the use of streptomycin has become widespread in the treatment of many infections in human beings, the question of its untoward side reactions assumes importance. To date, many reports of toxic reactions following its use have appeared in the literature.[1] One of the most constant of these reactions is temporary or permanent impairment of the eighth nerve apparatus.[2] No other neurologic involvement following streptomycin therapy has been reported. Local irritations at the site of injection,[3] fever,[4] dermatitis,[5] pruritis, rhinitis, conjunctivitis,[6] swelling of the buccal mucous membranes, flushes,[4] and eosinophilia have all been noted, either singly or in combination, and are considered manifestations of hypersensitivity to the drug. This report deals with 3 cases of painful stomatitis, at first resembling the aphthous variety, which developed during the treatment of pulmonary and extrapulmonary tuberculosis with streptomycin.

REPORT OF CASES

CASE 1.—L.B., a 55 year old man, was admitted to Montefiore Hospital on April 21, 1947, with the diagnosis of pulmonary tuberculosis. He had been in good health until midsummer of 1945, when he first noticed that his expectorations were occasionally streaked with blood. At that time, he had no fever, night sweats, thoracic pains or weight loss. A roentgenogram of his chest and an examination of his sputum revealed no abnormalities. He was asymptomatic for about one year and then noticed the gradual onset of fatigue and a slight loss in weight. In October 1946, a roentgenogram of the chest and sputum and bronchoscopic examinations revealed no abnormalities. In December, study of the sputum revealed acid-fast bacilli. Sudden hemoptysis, of about one-half glass of bright red blood, occurred on Jan. 14, 1947, and the patient was admitted to Morrisania Hospital, where he remained until his admission to Montefiore Hospital. In February, he received streptomycin for two and one-half weeks before its use was discontinued for nonmedical reasons.

The patient was known to have had diabetes for fifteen years, which was well controlled with insulin. He had had hemiparesis of the left side, for three years. There was no history of asthma, hay fever or urticaria. No one in his immediate family had allergic manifestations.

Physical examination revealed a slightly stout well developed white man in no discomfort, with no dyspnea, cyanosis or pallor. His chest was hypersthenic, with slightly diminished expansion on the right side. Fine rales were noted in the upper lobe of the left lungs, associated with harsh breath sounds and dulness to percussion posteriorly. There was slight facial weakness on the left and flexion paresis of the left forearm, with some atrophy of all the muscles of the left upper extremity. There was paralysis, of the upper motor neuron type, of the left lower extremity. Laboratory observations on admission were within normal limits. His sputum showed tubercle bacilli on direct smear.

Bed rest was prescribed until July 22, when 1 Gm. of streptomycin daily, 166 mg. every four hours, was prescribed. This dosage was maintained until August 26, when it was increased to 2 Gm. daily. On August 28, a generalized faintly erythematous nonpruritic finely papular rash developed, especially prominent on his back and abdomen. The next day he complained of pain in his mouth and throat, which was intensified by swallowing. At that time a few yellowish vesicles were visible on the mucous membrane of the cheeks, around the anterior pillars of the tonsils and on the inner surfaces of the lips. It was thought that this was nonspecific aphthous stomatitis, and warm saline gargles and the application of a solution of 1 per cent brilliant green in 50 per cent alcohol were prescribed. Despite medication, the vesicles eroded and were covered by a gray shaggy necrotic membrane. Smears and cultures revealed only a few fusiform and spirochetal organisms, in insufficient numbers to warrant the diagnosis of Vincent's disease. The presence of 10 per cent eosinophils on August 29 indicated the possibility of allergic stomatitis. The dermatologic consultant, Dr. Harry Keil, described the lesions as follows: Practically all of the buccal mucous membrane, as well as the vermilion portion of the lips, the undersurface of the tongue, the right pillar of the tonsil and extending into the pharynx, were sites of diffuse erosive stomatitis. The edges of some of the lesions showed a whitish membrane, but there was no definite evidence of bullae.

Treatment with streptomycin was discontinued on September 4, and remarkably rapid improvement occurred. In two days, the soreness and erythema had decreased, and within five days little evidence of the stomatitis remained. By this time the dermatitis had undergone fine desquamation on the back and extremities, with lamellar desquamation on the hands. Treatment with streptomycin was started again September 13, and after five doses (166 mg. every four hours) stomatitis, of the same character as previously described, recurred. In spite of cessation of treatment with the drug, it took fifteen days for all evidence of these oral changes to disappear. On September 18, the dermatologist stated that the disappearance of the eruption on the discontinuance of treatment with streptomycin and the recurrence of the stomatitis on retreatment with the drug, were definite proof for the correctness of the opinion that this was due to stomatitis streptomycin.

CASE 2.—R.D., a 47 year old white man, was admitted to Montefiore Hospital on April 8, 1946. He had apparently been well until about fourteen months prior to admission, when nonradiating pain developed in the middle of the upper part of the back. A diagnosis of "rheumatism" was made, and then increasing pain and limitation of motion called for further investigation. A roentgenographic diagnosis of tuberculosis of the vertebra (Pott's disease) was made, and the patient was admitted to the orthopedic service.

His past history revealed no pulmonary infections, asthma, hay fever or urticaria. His father had asthma, of unknown causation, for thirty years.

Physical examination revealed some tenderness to percussion in the region of the fifth to the seventh dorsal vertebrae. On admission a roentgenogram of his back showed a probable tuberculous abscess, involving the sixth and seventh dorsal vertebrae. On April 27, a body case was applied, with unsatisfactory results. A Hibb's fusion was performed on May 10, followed by an uncomplicated postoperative course. On August 16, some thoracic pain developed, and the patient produced blood-streaked sputum containing acid-fast bacilli. Examination revealed bubbling rales in the lower half of the right lung field. A diagnosis was made of erosion of a tuberculous mediastinal lymph node into a bronchus, with post hemoptoic

From the Pulmonary Division, Montefiore Hospital, New York.
The streptomycin was supplied by Merck & Co., Inc., Dr. J. M. Carlisle, Medical Director.

1. (a) Hattig, R. A., and Adcock, J. D.: Studies on the Toxicity of Streptomycin for Man: A Preliminary Report, Science 103:355-357, 1946. (b) McDermott, W.: Toxicity of Streptomycin, Am. J. Med. 2:491, 1947. (c) Riggins, H. M., and Hinshaw, H. C.: The Streptomycin—Tuberculosis Research Project, Am. Rev. Tuberc. 58:168-173, 1947.
2. Brown, H. A., and Hinshaw, H. C.: Toxic Reaction of Streptomycin on the 8th Nerve Apparatus, Proc. Staff Meet., Mayo Clin. 21:347-352, 1946. Molitor, H.: The Pharmacology of Streptomycin, J. Bact. 51:634-635, 1946.
3. Heilman, D. H.; Heilman, F. R.; Hinshaw, H. C.; Nichols, D. R., and Herrell, W. E.: Streptomycin: Absorption, Diffusion, Excretion and Toxicity, Proc. Staff Meet., Mayo Clin. 20:408-410, 1945.
4. Zintel, H. A.; Flippin, H. F.; Nichols, A. C.; Wiley, M. M., and Rhoads, I. E.: Studies on Streptomycin in Man: Absorption, Distribution, Excretion and Toxicity, Am. J. M. Sc. 212:421-430, 1946.
5. Heilman, Heilman, Hinshaw, Nichols and Herrell,[3] Buggs, C. W.; Pilling, M. A.; Bronstein, B., and Hirshfeld, J. W.: The Absorption, Distribution and Excretion of Streptomycin in Man, J. Clin. Investigation 25:94-102, 1946.

spread. His pulmonary condition responded to bed rest, and recovery was uneventful until early March 1947, when an afebrile painless swelling of the left side of the scrotum developed. A diagnosis of tuberculous epididymitis was made, and on May 17 a rupture to the outside occurred, with the formation of a tuberculous scrotal sinus. On June 13, 1 Gm. of streptomycin daily, in six equal doses, was prescribed and was followed by gradual healing of the sinus.

On September 18, the patient complained of a feeling of tightness in his lips, mouth and throat, with some difficulty in swallowing. There was slight swelling of the mucous membranes of the mouth. Within two days an aphthous-like eruption developed, closely resembling that described in case 1 (the figure). Stomatitis due to streptomycin was suspected, and

Appearance of lesions on the third day of stomatitis, after the patient (case 2) had had 1 Gm. daily of streptomycin for ninety-four days.

treatment with the drug was discontinued on September 23. The dermatologist confirmed the resemblance of this stomatitis to that in case 1. A culture taken from an eroded lesion revealed Staphylococcus albus and Streptococcus nonhemolyticus; no fungi were present. The lesion had completely disappeared by October 3. Streptomycin was readministered on October 6, with the immediate subjective response of itching and tightness of the mouth. Within three hours slight swelling of the buccal mucous membrane was evident, and in twenty-four hours oral lesions like the lesion first noted had developed.

Case 3.—S.S., a 50 year old white man, was transferred from Lebanon Hospital on Sept. 11, 1947, to Montefiore Hospital. Following pleurisy on the right side in 1937, a diagnosis of inactive minimal tuberculosis of the apex of the right lung was made. Roentgenologic studies and examinations of sputum were made at six month intervals, and for the first time, in January 1947, tubercle bacilli were seen in the sputum. Limited activity was prescribed until April, when, following a blow to his chest, substernal pain and shortness of breath developed. He sought no medical aid until July 2, when he was admitted to Lebanon Hospital with a diagnosis of coronary occlusion. The course of the disease was complicated by bilateral thrombophlebitis of the lower extremities and bilateral subdeltoid bursitis. On July 25, 2 Gm. of streptomycin daily were prescribed for his pulmonary infection. He had no untoward reactions until September 4, when dermatitis and painful stomatitis developed, but administration of the drug was continued until his admission to Montefiore Hospital.

Examination revealed a diffuse erythematous rash, with small reddish punctate papules. There were several small yellow vesicles in the mouth, predominantly on the inner aspect of the cheek and the vermilion border of the lower lip.

Because of the suspicion of dermatitis and stomatitis due to drugs, treatment with streptomycin was discontinued, and the lesions disappeared within a week. On September 17, 333 mg. of streptomycin were administered intramuscularly. Pruritus occurred immediately, and 50 mg. of tripelennamine hydrochloride ("pyribenzamine hydrochloride") was given, with relief of the symptom. Following administration of a similar dose of streptomycin four hours later, generalized erythema developed, with a mild chill followed by a temperature of 103 F., and oral lesions developed, similar to those described in cases 1 and 2. After cessation of treatment there occurred gradual improvement of the stomatitis.

COMMENT

The pertinent data of our 3 cases are summarized in the table.

Summary of Data in 3 Cases

	Case 1	Case 2	Case 3
Dosage (Gm. daily)	1 and 2	1	2
Total dose (Gm.)	39	94	84
Institution of treatment	7/22/47	6/15/47	7/25/47
Occurrence of stomatitis	8/28/47	9/18/47	9/4/47
Duration of stomatitis (days)	14	15	13
Eosinophils (percentage)	10	6	8

The clinical picture presented in the 3 cases was identical: painful, erosive and membranous stomatitis, involving the entire oral mucous membrane as well as the undersurface of the tongue. Aside from the relatively mild cutaneous eruption in 2 cases there was no association of other toxic symptoms.

When the oral lesions were first noted and the bacteriologic examination revealed no significant pathogenic agent, the possibility of stomatitis due to streptomycin presented itself; treatment with the drug was discontinued, and the lesions disappeared within fourteen days. The diagnosis was not certain, however, until retreatment with the drug caused a rapid reappearance of the lesions.

While it appears that stomatitis was a late rather than an early reaction, it was not possible to correlate the lesions with such factors as the daily dosage, the total amount of streptomycin given or the duration of its administration.

SUMMARY

Three cases of severe erosive and membranous stomatitis are presented, which occurred during the administration of streptomycin for the treatment of pulmonary and extrapulmonary tuberculosis.

This lesion healed rapidly after treatment with the drug was discontinued.

The fact that the lesions reappeared promptly on resumption of treatment with streptomycin indicated that the stomatitis was caused by the antibiotic.

ACUTE EXFOLIATIVE DERMATITIS AND DEATH FOLLOWING PENICILLIN THERAPY

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It is not within the scope of this paper to review in detail the various toxic reactions which result from penicillin sensitivity, as this information is readily available in any of the numerous publications on the subject, but rather to discuss a few of the more salient factors which should be borne in mind when one is called on to use this drug. Many reactions to penicillin or to the toxic impurities contained in individual batches of the extract have been described in the literature. Among these pruritus, urticaria, vesicular and bullous dermatitis, chills, fever, headaches and gastrointestinal disturbances have been particularly emphasized. Fortunately, none of these reactions are of such severity as to jeopardize the life of the patient. Whether the sensitizing agent in a particular instance is the active principle of penicillin or other substance in commercial penicillin capable of producing sensitization is not known, although it is generally conceded that the active principle of penicillin itself is the provocative agent.

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It is now a well established fact that persons who are allergic to penicillin may have a wide variety of toxic reactions. It is the purpose of this contribution to call attention to the more severe toxic effects of penicillin and report a case in which death followed its therapeutic administration. So far as our knowledge goes, no instance of death due to penicillin has been heretofore reported in the literature.

REPORT OF CASE

A. G., a white woman aged 72, was admitted to the Jewish Hospital because of pains in the right lower part of the abdomen diagnosed as acute appendicitis. At operation, a gangrenous and perforated appendix was found and removed. In addition, the peritoneal cavity was found to contain free, turbid fluid, which when cultured, yielded a nonhemolytic streptococcus. Because of the latter finding and as a safeguard against the spread of the peritoneal infection, she was given 400,000 units of penicillin daily in divided doses for eleven days. At the end of this time she recovered fully from the operation and was discharged from the hospital afebrile and feeling well; the wound of operation had completely healed.

Four days after her discharge from the hospital and seven days after the last injection of penicillin, the patient began to complain of a general body itch. This was soon followed by the appearance of a maculopapular eruption which covered almost the entire skin surface of the body. A punctate, erythematous eruption also appeared over the palate which was rather painful. The temperature rose to 102 F., the pulse rate was rapid and the patient appeared acutely ill. She was given adequate doses of diphenhydramine hydrochloride but with no beneficial effects. Within the next few days the rash became more pronounced and appeared confluent, first over the face, and later also, over the chest and the rest of the body. Diphenhydramine was then discontinued and tripelennamine hydrochloride was substituted, but again with no apparent improvement. The temperature continued to remain at a high level; she soon began to vomit and complain of abdominal pain and distention. She was then given "amytal" (N. N. R.) and ephedrine, but again with no alleviation of symptoms. The blood count showed 10,000 leukocytes, 76 per cent of which were polymorphonuclear leukocytes, 5 per cent eosinophils and the remainder lymphocytes.

The course of her illness was progressively in a downhill direction. Acute conjunctivitis developed with pronounced swelling and edema of the face. The mouth showed numerous small areas of ulceration covered with an adherent gray exudate. The skin over the face, and later also over the remainder of the body, began to exfoliate and presented a picture characteristic of acute exfoliative dermatitis. The lungs became congested, and a severe hacking cough developed which was most disturbing.

The patient was readmitted to the hospital acutely ill; she was stuporous and incontinent. Breathing was stertorous and the lungs considerably congested. Numerous moist rales could be heard almost over the entire chest. The body was covered with a homogeneous, fiery red rash with multiple areas of giant bullae; some of the latter had ruptured and discharged a clear, serous fluid. The clinical picture presented now by the patient was similar to that seen in cases of extensive second and third degree burns. For this reason the patient was given blood plasma alternating with 5 per cent dextrose solution intravenously, together with vitamin B complex, vitamin C and adrenal cortex extract. In spite of all medication, however, her condition grew steadily worse. The temperature began to spike at a high level, reaching a peak of 105 F. Many more skin blebs appeared, which soon ruptured, leaving behind large oozing surfaces. Also a generalized jaudice developed which became evident first over the sclera and later over the entire skin. Because of the pronounced swelling and ulcerations over the cubital veins, little blood could be obtained for detailed chemical studies. The blood urea was normal; the blood count and sedimentation tests showed no significant changes. The patient finally lapsed into a deep coma from which she could not be aroused; she died thirteen days after the first appearance of the toxic symptoms and the skin rash.

COMMENT

This case illustrates a severe type of reaction in a person who is allergic to penicillin. It is of interest to note in this connection that 2 of her children who received injections of penicillin for therapeutic purposes were equally sensitive to the drug and showed a most violent reaction. They both had headaches, nausea, vomiting, giant urticaria and fever which lasted for a period of three weeks before the symptoms subsided. Evidently, there exists here a familial sensitivity to penicillin. Unfortunately, this fact was not known to us at the time that the patient was treated with penicillin or careful scratch tests would have been done to determine the sensitivity of the patient to this drug.

The clinical picture presented by this patient merits some detailed comment, though in many respects it followed the pattern previously described by many authors. An analysis of the various case reports recorded in the literature, and of our own case, demonstrates rather clearly that there exists a latent period between the time of administration of the drug and the first appearance of symptoms. This time interval is estimated to be about five to twenty-one days; it was seven days in the present case. The ill effects of penicillin first became evident with the development of a general pruritus and the appearance of a cutaneous rash. In this respect the disease simulates closely other allergic reactions with cutaneous manifestations. The rash is not distinctive in itself and may be a macular, papular, urticarial, vesicular or bullous dermatitis. The vesicles have a tendency to rupture and leave behind raw, weeping surfaces. Cases of severe exfoliative dermatitis have been reported, most of which do not last more than three weeks. In the case under discussion the disease assumed a most fulminating character, causing death within two weeks following its onset.

While the cutaneous lesions dominate the clinical picture, other visceral manifestations may develop in the course of the disease and assume great significance. Of the various visceral disturbances, those affecting the gastrointestinal tract and the liver have received special emphasis. Many of the patients complain of general malaise, nausea, vomiting and abdominal pains. There are still numerous gaps in our knowledge of the precise nature of the anatomic changes produced in these organs by the action of penicillin. Unfortunately, permission for autopsy was denied in our case and therefore the exact nature of the pathologic changes produced by the drug in the various organs could not be determined. One is therefore reduced to speculation regarding the mode of action of penicillin on the gastrointestinal tract and other viscera. From our knowledge of the action of other allergins it may be surmised that similar anatomic lesions are also produced in the case of penicillin sensitivity. In the case of the gastrointestinal tract these changes consist of edema of the wall and sometimes also ulceration of the mucosa.

The development of jaundice in the course of treatment with penicillin suggests a hepatic lesion probably in the nature of a toxic hepatitis. Howells and Kerns[1] reported 47 cases of hepatitis in patients who were given injections of penicillin for venereal infections. These authors were not certain, however, that the penicillin was the direct cause of hepatitis. It was thought that the lesion in the liver was due to some icterogenic agent such as a virus, which was transmitted to the patient through faulty injection technique. There is no doubt however, that in the case under discussion the hepatitis was a direct result of the penicillin, to which the patient was unduly sensitive.

There is still considerable discussion as to whether the active principle of penicillin is the sensitizing agent, or whether some other substance present in commercial penicillin is capable of producing sensitizatoin. Most observers are of the opinion that the active principle of penicillin is the causative factor, and such proof has been offered through various scratch tests in the human being as well as animal experimentation. We are also inclined to believe that penicillin itself is the sensitizing agent, in view of the fact that similar toxic reactions were exhibited by 3 different members of the family, in whom different batches of penicillin were used.

The evidence now at hand seems to justify the conclusion that the haphazard use of penicillin is not devoid of risk. Fortunately, few patients react to the drug in a manner to lead to serious complications or to result in death. Most of the toxic

1. Howells, L., and Kerns, J. D. O.: Hepatitis After Penicillin Injection, Lancet 1:151 (Jan. 12) 1946.

reactions exhibited by patients treated with penicillin are mild in character and consist largely of a transient pruritus or urticaria. The case under discussion is perhaps the only one observed in which death followed the administration of penicillin. We do not believe that the amount of the drug or the length of time of its administration have any bearing on the various reactions attributed to its use; neither do we believe that the method of its administration has any significant effect on the clinical picture. Toxic reactions of all degrees of intensity have been observed independently of whether the drug has been given in smaller or larger doses or whether it was administered parenterally or applied topically. Numerous observations made on allergic persons, as well as experimentally on animals, have confirmed these findings.

The present study indicates the need for a careful study of patients subjected to penicillin therapy, especially when there is a familial history of allergy. The haphazard use of penicillin appears to be not entirely free of danger, and serious complications may be avoided by the more careful and controlled use of the drug.

SUMMARY

A case is presented in which death followed the parenteral administration of penicillin. The various toxic manifestations of penicillin sensitivity are reviewed and discussed. It is suggested that great caution should be exercised in the routine treatment of patients with penicillin, especially when there is a history of allergy and when the patient is elderly.

"MESANTOIN" POISONING WITH APLASTIC ANEMIA AND RECOVERY

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and
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Since 1945, Loscalzo [1] and Kozol [2] have enthusiastically advocated "mesantoin" (3-methyl-5, 5-ethylphenylhydantoin) in the treatment of "grand mal" epilepsy. Investigators in other clinics, Clein [3] and Fetterman, [4] have confirmed their results, and it would seem that a rather harmless, wonderfully effective drug was now available for the control of "grand mal" attacks.

Swinyard and Goodman [5] have noted that "mesantoin" was less toxic than "dilantin sodium" (diphenylhydantoin sodium) in rats, and Kozol [2] reported the ingestion of 7.2 Gm. of "mesantoin" in a suicidal attempt without any serious after-effects. The toxic effects of diphenylhydantoin sodium, such as gingival hypertrophy, cutaneous rash and drowsiness, occurred at times following "mesantoin," but were always less severe.

The chemical formulas of the various anticonvulsant drugs are similar (fig. 1). Diphenylhydantoin and "mesantoin" are both derivatives of hydantoin, but differ in that "mesantoin" has an ethyl group in place of one of the phenyl groups on carbon no. 5 of diphenylhydantoin and also has a methyl group on nitrogen atom no. 3. Trimethadione is not a hydantoin derivative but is related in structure to "mesantoin" in that an oxygen atom has been substituted for the no. 1 nitrogen of "mesantoin" and two methyl groups have been substituted for the ethyl and phenyl groups on carbon no. 5. "Mesantoin" seems to be less toxic, but it is a hydantoinate, and in persons sensitive to this chemical group abnormal reactions should be expected. We are reporting a case of sensitivity to "mesantoin" followed by aplastic anemia and recovery.

REPORT OF CASE

Mrs. C. S. G., a white woman aged 34 years, consulted us in October 1946, complaining of "grand mal" seizures with psychomotor automatisms since the age of 5. During the next three years of her life she averaged two attacks weekly. A strict dietary regimen relieved the attacks for four years. At the age of 12 the menarche started and the seizures returned. Anticonvulsant therapy had some effect, but the attacks still occurred twice a year. The patient married at the age of 20. She continued with "grand mal" seizures which were more severe during menses. She had two normal pregnancies and both of her children were apparently healthy. In 1944, when 31, she underwent a hysterectomy and salpingo — oophorectomy for leiomyomas of the uterus. Later that year her gallbladder was removed after acute cholecystitis. She had been under the care of numerous physicians, and various anticonvulsant drugs, such as "mebaral" (N — methyl phenobarbital), phenobarbital, and diphenylhydantoin sodium, had been given with only fair results. During 1946, she was taking 6 grains (0.4 Gm.) of diphenylhydantoin sodium daily, but her convulsive attacks occurred every two weeks. Her general health was excellent. There were no unusual gastrointestinal, cardiorespiratory or genitourinary symptoms.

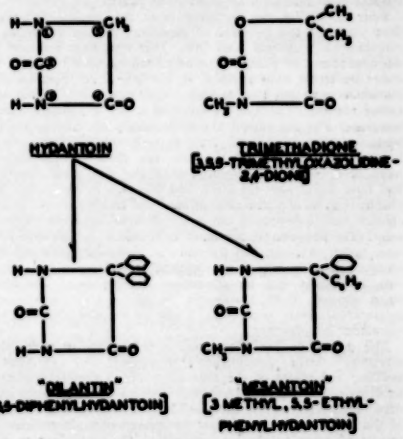

Fig. 1.—Chemical formulas of various anticonvulsant drugs.

The patient described the attacks in this manner. She would have a sensation of coldness, followed by stiffness with a drawing up of her hands. There was frothing at the mouth, biting of the tongue and at times incontinence of urine. On awakening from the attacks, the patient felt hazy and complained of a dull headache. In the last months of 1946 severe, incapacitating headaches developed not related to the convulsive seizures.

Physical Examination, October 1946.—The patient was a slender, alert, intelligent woman with no evidence of mental deterioration. There were no pathologic reflex changes. The eyegrounds were normal. The heart and lungs were normal. The blood pressure was 104 systolic and 70 diastolic. There were healed abdominal scars. The extremities were normal. The laboratory studies revealed normal urine. The hemoglobin was 88 per cent, the erythrocyte count was 4,500,000 and the leukocyte was 7,400, with 68 per cent neutrophils, 31 per cent lymphocytes and 1 per cent mononuclear cells. An electrocardiogram was normal.

The patient was referred to Dr. Harry Brick for further investigation of her epileptic seizures. He noted that her mental status was that of a congenial, alert, dejected and tense person. The patient listened to questions intelligently and responded coherently. She was oriented as to time, place and person. Her remote memory was good and recent memory fair. Retention was adequate. Judgment and insight were not impaired. The patient complained of diminished concentration; she worried a great deal, was upset easily and was sad and unhappy. At times she entertained ideas of self destruction. There was some feeling

From The Department of Medicine, Medical College of Virginia, and St. Luke's Hospital.

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of self depreciation and inadequacy but no psychiatric content could be elicited.

The patient's developmental history revealed a good home background, with much indulgence by her family. She was the oldest of five children, with no stigmas of epilepsy in the rest of her family. She had reached the second year of college and was interested in dramatics and voice. Her school attendance was irregular on account of the seizures.

Electroencephalograms in December 1946 and in March 1947 showed questionable slow waves but no convulsive patterns. In February 1947, the patient was started on 0.2 Gm. of 'mesantoin" daily. She had no convulsive seizures of any kind and remained in excellent health, with normal hematologic studies every two months. On October 17 a severe incapacitating headache developed, followed by unusual drowsiness. Her gums began bleeding and for a week the headaches and drowsiness increased. The patient, by her own volition, increased the "mensantoin" to 0.3 Gm. daily. She presented herself to Dr. Brick after an absence of three months, on October 27, and at that time she was weak, pale, drowsy, with bleeding gums and subcutaneous hemorrhagic nodules on both lower extremities. The "mesantoin" was immediately discontinued and hematologic studies revealed a scarcity of all elements. The erythrocyte count was 2,370,000, hemoglobin 47 per cent, white blood cell count 1,550, with 10 per cent neutrophils, 79 per cent lymphocytes, and 2 per cent mononuclears cells. The patient was admitted to St. Luke's Hospital on November 10.

Clinical Course in the Hospital.—On admission to the hospital the patient was apparently acutely ill, apprehensive, but rational and cooperative. There were pronounced pallor and bilateral subconjunctival hemorrhages. The temperature was 102 F., pulse rate 100 and blood pressure 100 systolic and 60 diastolic. The eyegrounds were normal. There was profuse bleeding from the gums, with decided gingival hypertrophy. There were no ulcers in the pharynx. The tissues about the lower jaw were edematous. The heart and lungs were normal. The spleen and liver were not palpated. Petechiae were diffusely distributed over the entire body, and tender nodular contusions were present on both tibiae.

Laboratory examinations revealed hemoglobin 36 per cent Sahli (17 Gm. being used as standard), red blood cell count 2,040,000, white blood cells 700, with only 25 cells seen in whole field. Six were neutrophils and 19 lymphocytes. There were no reticulocytes. The platelet count was 70,000. The blood was type B, Rh positive. The Eagle serologic test was negative in result. Sternal puncture done on November 12 was reported by Dr. J. H. Scherer as follows: Sternal puncture showed a smear which was not greatly different from the peripheral blood. In looking over two smears, 1 normoblast was seen. There was a rare myelocyte, occasional reticulum cells and scattered polymorphonuclear leukocytes and lymphocytes. No platelets or megakarocytes were seen. This is the most aplastic marrow that I have ever seen.

The urine was essentially normal.

The patient was started on daily transfusions of fresh whole blood, and 50,000 units of penicillin was given intramuscularly every three hours. On November 26, 125,000 units of streptomycin was given intramuscularly every three hours. "Pentnucleotide" was given intramuscularly three times daily, but was discontinued after several days because of pain at site of injections. In addition, the patient was given 2 cc. of crude liver extract intramuscularly, twice daily for one week, and 150 mg. of pyridoxine and 15 mg. of folic acid were given orally, daily through hospital stay of fifty-nine days.

The temperature varied from 100 to 103 F. daily, with frequent rises following the blood transfusions. The patient continued to bleed profusely from the gum margins and remained drowsy. The transfusions caused a rapid rise in hemoglobin, but there was a negligible response in the white blood cells. After a week, she began complaining of severe rectal pain and was found to have a large rectal abscess which was incised and drained a profuse quantity of dark, bloody, purulent material. At this time the patient was in extremis. She was irrational, taking little nourishment; small hemorrhages were seen over the entire body, and every needle puncture was followed by a subcutaneous hemorrhage. The patient was given gradually increased doses of sodium bromide, ranging from 20 to 30 grains (1.3 to 2 Gm.) three times daily, in order to combat any convulsive seizures. Signs of bromidism developed after a month and the blood bromides rose to 173 mg. per hundred cubic centimeters. On discontinuance of the drug and on administration of sodium chloride, the bromide level gradually dropped to 31 mg. per hundred cubic centimeters. On December 3, twenty-four days after admission, her hematologic picture suddenly improved and there was an increase in the neutrophils to 20 per cent. Her delirium subsided, the rectal lesion began healing, the gums were less friable, and the temperature subsided to normal. The patient began eating and continued to improve. There was occasional bleeding from the gums and crops of petechiae on the lower extremities. Figure 2 represents the hematologic studies and

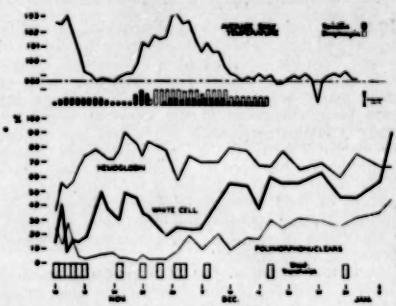

Fig. 2.—Clinical course of patient C. S. G.

temperature reaction with the various doses of penicillin, streptomycin and the transfusion intervals.

The patient has been in excellent spirits and had no recurrence of seizures since leaving the hospital. She had been maintained on small doses of chloral hydrate and phenobarbital. It has been necessary to administer two transfusions, but she has definitely improved and the last hematologic studies, on Jan. 28, 1948, revealed: hemoglobin 64 per cent, red blood cell count 2,900,000, white blood cell count 4,100, with 51 per cent polymorphonuclear neutrophils and 49 per cent lymphocytes. The platelet count has risen to 150,000.

COMMENT

Harrison, Johnson and Ayer[6] recently described a fatal case of aplastic anemia following the use of trimethadione and "mesantoin." They believed that trimethadione was the causative agent because at that time "mesantoin" was considered an innocuous preparation. The findings in our case suggest the possibility that "mesantoin" was the responsible toxic factor or at least a contributing one in their patient. The many favorable reports on "mesantoin" in the treatment of "grand mal" epilepsy indicate that probably only a few persons are sensitive to this hydantoin, but when anticonvulsant therapy is started it must be continued over a long period, and even the finding of 1 sensitive person should lead to a conservative policy when this drug is utilized. It is our suggestion that with any of the hydantoinate group, hematologic studies be performed at least once a month and any sudden drop in the hemoglobin or granulocytes should be viewed with suspicion. Patients receiving these drugs must be warned of the necessity of frequent blood studies.

CONCLUSION

This is a report on development of severe aplastic anemia with hypoplastic bone marrow in a patient sensitive to "mesantoin"; finally the patient recovered after numerous transfusions, penicillin, streptomycin, and various hematinic aids.

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Council on Foods and Nutrition

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JAMES R. WILSON, M.D., *Secretary*

CALORIC UNDERNUTRITION AND STARVATION, WITH NOTES ON PROTEIN DEFICIENCY

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1. INTRODUCTION

Justifiable enthusiasm about discoveries of specific nutrients and their metabolic consequence has distracted attention from the oldest problem in nutrition—simple caloric inadequacy. General undernutrition, with or without major deficiences of individual nutrients, has always been widespread in the world at large; the tragedy of famine periodically emphasizes how slender is the margin of safety. In the United States and Canada food production has been so abundant for many years that the direct impact of famine is unknown; the consequences of food shortages elsewhere, however, increasingly demand attention and effort here. Moreover, the importance of secondary undernutrition in disease is beginning to be realized.

Caloric undernutrition has been generally assumed to involve a parallel protein deficiency in most cases. In Asia, the area of most frequently recurring famine, the diet is low in protein in the best of times. Any food shortage quickly reduces such sources of proteins as are usually available, and subsistence depends almost entirely on rice, tapioca and other foods which contain little protein. In Europe the protein in the typical famine diet is almost all of vegetable origin. In any case, the severely undernourished person is necessarily in a state of negative nitrogen balance so there is at least some of the effect of a protein deficiency. The present discussion includes some remarks on protein deficiency (sections 7, 8 and 9).

Practical questions about general undernutrition raised by World War II clearly revealed the undeveloped state of this area in the science of nutrition. Generalities about metabolic balance, normal weight for height, and optimal food intakes are of small help in evaluating the actual degree of caloric inadequacy, in predicting the consequences of a specific dietary level and in planning and operating programs of relief and rehabilitation. This is a field in which the contribution of animal experimentation is necessarily small; quantitative translation from animal to man is dubious at best and impossible in terms of behavior, intellective functions, work performance and many details which have great medical and social significance. The residue of useful data on man himself is surprisingly meager but has been greatly augmented in the past few years.

2. SOURCE OF INFORMATION

Limitations of animal experiments have been mentioned; besides the interpretive difficulty, the actual evidence from studies on animals is not great. On man there is a plethora of general impressions and observations from famine areas; besides frequent deficiencies in technical measurement, these reports usually provide only a description of the famine victims without information about their prestarvation characteristics or satisfactory details as to the dietary intakes which produced their present condition. The same strictures may be made about the clinical literature on cachexia. From a vast literature, however, many common points emerge; for the most part these can only be incorporated, without specific citation, in the present summary.

Studies on a few fasting persons constitute the classic literature cited under "starvation" in the textbooks. Acute experiments with no food at all are of great interest, but they have only relatively remote bearing on the problems of chronic undernutrition and the real conditions of famine. Another question is whether the professional fasters and fanatics who have been studied are reasonable representatives of the general population.

There have been two major experiments on prolonged undernutrition in man. The Carnegie Institute experiment [1] provided much information from a group of young men who voluntarily submitted to underfeeding for several months; the degree of semistarvation was small, as indicated by weight losses of only the order of 10 per cent. In the Minnesota experiment 32 young men lost an average of 24 per cent of their body weight in six months; the total period of study lasted almost two years.[2]

There are no recent full-dress reviews of undernutrition and starvation, but several older works are still of great value: Porter [3] for a first-hand account, with many autopsies, of famine in India; Lusk [4] for the metabolic problems; Morgulis [5] for a discussion from the point of view of the biologist, and Jackson [6] for an exhaustive treatment of morphologic aspects. Several recent papers provide good general pictures. Leyton [7] reported observations in a prisoner of war camp where there were some elements of scientific control. Data on weight changes and mortality of internees in France are valuable.[8] Summaries of data on occidental persons starved in Japanese camps are available.[9] Useful vital statistics and estimates of dietary intakes in periods of famine are provided for Holland [10] and for Greece.[11] Data from the siege of Leningrad are interesting.[12]

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The present review is mainly an abstract of parts of a book, "The Biology of Human Starvation," which will be published by the University of Minnesota Press in 1948. The greatest single source of data is the Minnesota experiment (1944-1946). Both book and experiment are the joint works of Dr. Ancel Keys and Drs. Josef Brozek, Austin Henschel, Olaf Mickelsen and Henry Longstreet Taylor, with assistance on various phases by Miss Angie Mac Sturgeon and Drs. Samuel Wells and Ernst Simonson.

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3. EUROPEAN AND ASIATIC FAMINE

The details of the effects of caloric undernutrition are modified by many factors, including particularly the previous state of nutrition, the character of the inadequate diet and the presence of intercurrent disease. In spite of individual and local variations, certain patterns seem to be characteristic of European countries on the one hand and Southeastern Asia on the other.

In the European countries, especially the northern and central regions, food shortages generally result in a diet dominated by whole or undermilled grains (mainly wheat), potatoes, turnips, cabbages and garden vegetables. The result frequently is a diet which is surprisingly good, qualitatively, and deficiencies in vitamins and minerals may not be prominent. The protein content is not vanishingly small and ordinarily comprises something like 10 per cent of the calories.

The diet in Asiatic famine tends to depend on starchy and fibrous foods, which are often exceedingly poor sources of proteins, vitamins and some minerals. The common frequency of endemic infections and infestations in Asia is exaggerated under famine conditions. The combinations of these debilitating conditions are endless, but those which most frequently modify the picture of simple caloric deficiency are hypoproteinemia, anemia, dysentery and deficiencies of some of the vitamins. Famine in Asia is attended by more severe edema and anemia and more frequent neuropathic conditions than in Europe. The present review cannot treat of these complications; it deals primarily with the simpler European type of undernutrition.

4. THE INCIDENCE OF GENERAL UNDERNUTRITION

A large incidence of general undernutrition seems to be an inevitable companion of national poverty, and this is chronically the state of affairs in most of Asia and large sections of Africa, Southeastern Europe, Central and South America. Until recently general undernutrition was frequently the lot of the underprivileged or economically unfortunate classes everywhere; crop failures or economic depression quickly resulted in semistarvation for the poor. In the United States this situation, never very pronounced, seems to have disappeared. In the great depression beginning in 1929 there was little caloric inadequacy and practically no starvation. In this country severe general undernutrition because of inability to obtain food does not exist except by peculiar accident for isolated persons; there is no reason to believe that this situation will change.

This does not mean that there is no general undernutrition in the United States. There are recluses, invalids, children and aged persons who are unable or unwilling to disclose their want and who may be missed by the proper governmental or charitable organization. Probably far more numerous are the persons who are generally undernourished because of the presence of disease. Anorexia of some degree is undoubtedly far more common than indicated by the rare cases diagnosed as anorexia nervosa or Simmonds' disease (hypopituitary cachexia). Undernutrition is prominent in the majority of patients with advanced neoplasms. Temporary undernutrition results from most severe infectious diseases and from major injuries and surgical operations.

The question of the incidence of caloric undernutrition in the general population has been raised by the results of some surveys of dietary intake. On the basis of one or another caloric yardstick, termed proper, ideal, adequate, recommended, optimal or required, comparisons are made with the estimated actual intake: if the latter value is less than the theoretic standard the case is labeled caloric insufficiency. Thus Wiehl [13] studied the diets of 1,080 aircraft workers and concluded that "the evidence is strong that a considerable number of these men were below a consumption level believed to be adequate." Further, this author commented on dietary surveys in Toronto, Ontario, and Halifax, Nova Scotia, Canada, to conclude that "it is not unusual for wage earners to eat a diet with less energy than is deemed desirable." [14] The absurdity of conclusions derived from this approach is revealed by data on high school pupils.[15] More than half (55.3 per cent) of these pupils were judged to be calorically undernourished, but analysis of the physical examination data shows that of these undernourished children only 11.1 per cent were underweight while 47.7 per cent of them were overweight by 7.5 per cent or more.[16]

5. CALORIC REQUIREMENTS AND RECOMMENDATIONS

The term caloric requirements is widely used, but so far has escaped precise definition, nor will this be attempted here. With any reasonable definition the requirement will be dependent on body size, age, sex, climate, occupation, personal habits, previous state of nutrition and perhaps race.

It is not possible to draw a fine line between caloric adequacy and general undernutrition, least of all by using the caloric intake alone as the criterion. In a given person caloric balance can be maintained over a rather wide range of body weight and caloric intake, and it is not now possible to conclude whether, in the long run, the optimal condition would be toward the upper or lower end of a range amounting to perhaps 10 per cent or more of the average body weight. Changes in body weights are a different matter, and a person not previously obese who loses 10 per cent or more in weight and continues to lose weight is clearly calorically deficient; roughly the same criterion may be applied to the averages for populations.

Various authorities (e.g., the League of Nations and the National Research Council) have made recommendations regarding caloric intake. These are useful in comparing populations and in planning food production; such validity as they have is that of broad averages, and their application to individuals is unwarranted. By and large, the caloric recommendations of the League of Nations and of the National Research Council may be rather higher than optimal. Slight to moderate decreases in per capita consumption below these recommendations in England and Switzerland in World War II and after were associated with evidences of better health. The role of changes in quality of food in these results is obscure, but certainly no adverse effect can be claimed from the caloric reductions. Fleisch [17] concluded that instead of a required average of 2,400 Calories for sedentary adults, the experience of World War II showed an average intake of 2,160 Calories to be sufficient and even beneficial in Switzerland. In the United States careful studies on caloric intake reveal surprisingly low values in some instances where there is no clinical indication of inadequacy.[18]

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6. FASTING AND ACUTE STARVATION

Both fasting (total abstinence from food) and prolonged undernutrition result in many similar effects such as bradycardia, lowered metabolic rate, hypotension and weakness. But there are also obvious important differences; a few of these may be noted simply to emphasize the point that results in fasting experiments cannot be applied in any detail to problems of chronic undernutrition. Prolonged fasting has its intrinsic scientific interest, but it is rarely encountered in nature.

All reports on fasting are in agreement that the sense of hunger quickly disappears as the fast is continued. If the subject is sedentary, hunger is seldom disturbing after the third day and is usually entirely absent in a week. This loss of hunger is much accelerated by physical work. In experiments in the Laboratory of Physiological Hygiene fasting young men doing hard physical work lost the sensation of hunger in twenty-four hours and incipient nausea, with the attendant revulsion to food, was troublesome on the second or third days. This is in sharp contrast with undernutrition in which the sense of hunger progressively increases until it occupies a major part of the consciousness. Only near the termination with death from starvation does the condition change to resemble that in total fasting. Besides such differences in physical sensation, there are decided tendencies to differences in emotional state. Depression and apathy are almost universally observed in persons with severe undernutrition but in sedentary fasting euphoria and states of excitement are not uncommon.

It may be presumed that fasting is a greater, certainly a more abrupt, emergency and therefore a stronger stimulus to mobilize defense mechanisms in the body. This, together with the simple factor of time, may account for some differences in the blood chemistry compared with that in chronic undernutrition. The concentration of both erythrocytes and leukocytes in the blood of fasting persons tends to remain within relatively normal limits, though subject to variations from time to time. Simple undernutrition, however, tends to produce a leukopenia and a progressive anemia.

Perhaps the most striking differences between total and partial inanition are related to the differences in carbohydrate metabolism. Only a small supply of exogenous carbohydrate (which may be supplied also from exogenous protein) suffices to prevent ketosis. The amount required for this—of the order of 600 Calories per day—is usually obtained even in the worst conditions of famine. In any event, ketosis and ketonuria do not ordinarily appear in chronic undernutrition but pronounced ketosis develops in a few days of fasting. Associated with this difference in respect to ketosis are differences in the respiratory quotient, in acid-base balance and in the blood sugar level.

In the studies in the Laboratory of Physiological Hygiene there were observed interesting differences in the relative resistance of various functions to fasting on the one hand and to prolonged undernutrition on the other. For example, strength, as measured in single maximal exertions, is relatively resistant to fasting but is definitely reduced by prolonged underfeeding. In contrast, the coordination of movements is more strikingly reduced by fasting than by semistarvation.

7. PROTEIN DEFICIENCY AND REQUIREMENTS

Pure protein deficiency, with adequate calories and vitamins, is probably seldom encountered in nature, and little is known about it in man. That it retards or reverses growth and leads to hypoproteinemia and anemia is clear. In Asia it contributes to the picture of famine edema and probably frequently complicates the decision as to whether there is a major deficiency of calories or thiamine. Protein deficiency will be considered here mainly as it may be associated with general undernutrition or may be confused with it.

Where caloric inadequacy exists the importance of the protein intake is dubious because the protein tends to be used as fuel in place of fat and carbohydrate and thereby is deprived of its ordinary important function. At exceedingly low levels of caloric intake—below 1,000 Calories daily for an adult—the substitution of protein for carbohydrate in the diet has practically no effect on the balance and the net nitrogen loss from the body continues. At higher but still inadequate levels of caloric intake it may be that dietary protein may spare some nitrogen loss, but the evidence is not fully satisfactory.

As in the case of calories, the concept of protein deficiency also involves consideration of protein requirements; presumably deficiency exists when requirements are not met. The situation is more complicated with proteins than with calories because there are several modifying factors. On the other hand, the criteria for establishing protein requirements are, at first glance, simpler and more objective.

In the growing animal it is customary to consider the least amount of protein which will allow the maximal rate of growth to be the requirement. Clearly this is the requirement for maximal growth, but for what else? Whether this level is optimal is an abstruse question which is seldom asked and which, actually, may be unanswerable without more precise definition. Optimal for what? In the case of animals the only values which are readily examined are size and appearance, physical health—meaning merely the absence of disease and defects—and longevity. The latter is infrequently considered, perhaps because the small evidence available points to an inverse correlation between rate of growth and eventual longevity. Numerous factors of great human value which may be affected by the level of protein nutrition are almost never considered, let alone evaluated.

In the adult the usual criterion for the protein requirement is the least intake level which will maintain nitrogen balance. In practice the method is more troublesome than in theory because of the tendency to spontaneous variation and the difficulty of obtaining exact balance. The expedient of measuring nitrogen excretion in fasting or on a protein-free diet is used to get a minimal estimate of the endogenous protein destruction, but this does not tell how much intake of a particular protein or protein mixture will result in nitrogen balance.

Labile protein reserves (depot nitrogen) in the body are generally considered to be very small, and a sizable negative nitrogen balance for more than a day or two is taken to mean tissue depletion or destruction. But there are situations in which a negative nitrogen balance seems to be physiologic or at least difficult to avoid and perhaps harmless.

8. NITROGEN BALANCE AND PHYSICAL ACTIVITY

Protein catabolism is not increased in muscular exercise; the protein requirement is not altered by participation of protein in the direct energetics of physical activity. This does not mean that the nitrogen balance and requirement are independent of the activity in the long run.

In bed rest, which is the most frequently prescribed therapy in all forms of disease and injury, the nitrogen

balance quickly becomes negative on any ordinary diet and this occurs even in the absence of disease or injury; on the resumption of normal activity the nitrogen balance of the patient becomes positive. This phenomenon would seem to be a kind of disuse atrophy; probably most of the nitrogen lost comes from muscle cytoplasm and there may be no actual cellular destruction, at least at first. Similarly, chronic intensification of activity and muscular exercise calls for increased sarcoplasm and therefore nitrogen retention (exercise hypertrophy). It is puzzling, however, to find that even in bed rest and in the presence of situations that involve destruction of tissue there may be a positive nitrogen balance if the protein intake is forced to extremely high levels.[19] Decreases in hemoglobin and plasma protein may occur in infections even when nitrogen retention is good.[19a]

Somewhat similar difficulties arise from the fact that a definitely positive nitrogen balance in adults may be induced by some hormones, notably testosterone propionate. It is difficult to avoid the conclusion that the old discussion of protein reserves must be reopened. Since no specific reservoir of labile protein can be found, it may be suspected that the tissue cells in general have some nitrogen reserve and storage capacity.

In any case, the concept of protein requirements seems less simple and precise than might have been hoped. The optimal protein intake may be something else again, but there is little evidence as to quantitative relationships. The recommendations of many authorities, including the League of Nations and the National Research Council, tend to fix on 1 Gm. of protein per kilogram of body weight for adults. But in studies on young men doing hard work in the open no advantage was found for intakes greater than about two-thirds this amount, even when much of the protein was from vegetable sources.[20] This tends to be in agreement with recent careful studies on nitrogen balance, in which it was concluded that the National Research Council recommendation for a 70 Kg. man could be reduced to 50 Gm. and still provide approximately 30 per cent margin above requirements.[21]

The conclusions indicated in the preceding paragraph will be challenged by those who believe that neither crude nitrogen balance nor performance in normal health tell the whole story. Large excesses of protein intake have been suggested to be advantageous in building up reserves or antibodies, which may be called on to meet the emergencies of disease or injury. The evidence is still controversial except in the case of persons who have been in negative nitrogen balance and in whom a period of positive balance may be restorative. But elevated protein intakes are not clearly detrimental, though they are expensive, and will undoubtedly be recommended by many nutritionists to be "on the safe side."

9. PROTEIN QUALITY

Long ago animal feeding experiments with different individual proteins demonstrated differences in quality; the protein requirement was different for the several proteins. Some of the vegetable proteins were notably inferior to the animal proteins, and it became customary to believe that a considerably greater intake of vegetable proteins was required as compared to animal proteins. Some of this difference could be traced to differences in digestibility and absorption, but more important discrepancies were related to metabolic utilization. It is now agreed that the last is dependent on the amino acid composition of the proteins. Inadequacy of one essential amino acid limits the synthesis of the tissue proteins which must contain it and thereby leaves excesses of the other amino acids which are then useless for this purpose. Accordingly, general protein deficiency may result from lack of a single amino acid.

In actual practice, that is, under the great majority of natural conditions, the importance of protein quality is much less than previously supposed. In ordinary diets, even of the vegetarian type, the protein moiety is made up of many different proteins and the chance that all of them will be low in one or more amino acids is small. On diets of limited variety, however, it is possible to have conditions like the earlier rat experiments in which substantially all the protein is supplied by a very few proteins. Such a condition may easily arise in famine areas; in such cases the provision of small amounts of foods rich in the missing amino acids may be highly beneficial.

An example of unsuspected amino acid deficiency and an interrelationship with a vitamin has recently emerged in pellagra. It now appears that pellagra may result from a deficiency in either tryptophane or nicotinic acid and may be successfully treated by either the amino acid or the vitamin.[22] This means that the protein requirement may be altered by either its tryptophane content or by the amount of nicotinic acid in the diet. It is entirely possible that other similar relationships between amino acids and vitamins will be discovered. The protein requirement is certainly not an independent entity.

10. THE PROBLEM OF BODY WEIGHT AND FAT

Caloric inadequacy produces a weight loss or a low level of weight for height. In practice, dependence in diagnosis is usually on the height-weight relationship; this means comparison with some set of standards. It is essential to recognize the derivation and limitations of such standards. Since there are as yet neither theoretic nor experimental bases for establishing ideal or optimal relationships between height and weight, recourse is had to averages of supposedly healthy groups which are taken as the standards. The body weight of a given person is then compared with the average of a group of healthy persons of the same sex, age and height. The difference between the individual and the group average is then expressed as pounds overweight or underweight. As an added refinement allowance may be made for body build or type, with standards being broken down into groups such as large frame and small frame. There is no agreement as to how these body types may be properly segregated.

Regardless of refinements of measurements and classification, all these standards involve some major uncertainties. First, the designation healthy in the reference group means only the absence of obvious disease and defect, and all persons in the reference group are presumed to be equally healthy, a presumption without basis and certainly false if it is admitted that health has gradations. Second, it is assumed implicitly that

19. (a) Sprunt, H. Y.; Evans, E. I., and Forbes, J. C.: The Influence of Special High Protein Diet on Protein Regeneration in the Surgical Patient, Ann. Surg. **124**: 131-141, 1946. (b) Howard, J. E., and others: Studies on Convalescence: Nitrogen and Mineral Balances During Starvation, and Graduated Feeding in Healthy Young Males at Bed Rest, Bull. Johns Hopkins Hosp. **78**: 282-307, 1946.

20. Darling, R. C.; Johnson, R. E.; Pitts, G. C.; Consolazio, F. C., and Robinson, F. P.: Effects of Variations in Dietary Protein on the Physical Well Being of Men Doing Manual Work, J. Nutrition **28**: 273-281, 1944.

21. Hegsted, D. M.; Tsongas, A. G.; Abbott, D. B., and Stare, F. J.: Protein Requirements of Adults, J. Lab. & Clin. Med. **31**: 261-284, 1946.

22. Krehl, W. A.; Teply, L. J., Sarma, P. S., and Elvehjem, C. A.: Growth-Retarding Effect of Corn in Nicotinic Acid-Low Rations and Its Counteraction by Tryptophane, Science **101**: 489-490, 1945. Salmon, W. D.: Relation of Corn Products to the Requirement of the Rat for Dietary Nicotinic Acid, J. Nutrition **32**: 169-175, 1947.

the average somehow connotes the best; this is a nice democratic arrangement but scarcely scientific.

Presumably, the main concern in all examinations of height and weight is the proportion of the body represented by fat. In very emaciated and in very obese persons the principal difference is in the amount of fat, and this may be roughly gaged by the gross weight. Outside of these extremes, however—and it is precisely with less extreme cases that the real interest lies—the relation of fat to weight is far less exact.

The body fat may be estimated from its specific gravity, taking advantage of the low density of fat.[23] When this is done with a group of ordinary men, with no great extremes of emaciation or obesity, there is no correlation between true fatness and the degree of overweight or underweight calculated from height-weight tables.[24]

11. WEIGHT LOSS IN UNDERNUTRITION

Reliable data on weight losses in famine and chronic undernutrition are remarkably few. The person who is semistarved against his will almost invariably overestimates his prestarvation weight and his weight loss. The same is often true of persons on reducing diets.

As noted previously, true ideal weights are not known and it is not possible to define precisely the level at which weight loss or departure from standard average becomes important. Probably deviations of less than 10 per cent below standard average weight-for-height are of small moment per se. On the other hand, a sudden weight loss of as much as 5 per cent may be significant. Weight losses of 10 per cent or more that are brought about in a few months in persons not previously obese involve definite impairment in endurance and working capacity and are associated with adverse changes in personality and emotional status.

In previously healthy young adults weight losses up to about 30 per cent can be tolerated with every prospect of eventual full return to normal with proper rehabilitation care. The lethal level is generally around a 40 per cent weight loss, though instances of losses of 50 per cent of weight, with recovery, have been recorded. In severe semistarvation the true weight loss may be difficult to estimate because of the presence of edema; the foregoing figures are for gross weight, including the ordinary amount of edema. When there are exceptionally pronounced edema and ascites, the lethal point may be reached with weight losses of only 20 to 30 per cent.

The rate at which weight is lost in undernutrition is of consequence. In general, it seems that the more rapid the weight loss the more serious is the disability at equal total weight losses. This is a point of both theoretic and practical interest which deserves special study. Allied to this problem is that of adaptive and compensatory phenomena in persons who are habitually underweight in comparison with ordinary standards.

12. MORPHOLOGY: BONES AND TEETH

The bony structures of the body are relatively resistant to caloric undernutrition. No adverse effect on the formed teeth has been objectively demonstrated in either acute or chronic starvation. The bones, however, are not totally immune from change. Hunger or famine osteopathies have been reported many times in both European and Asiatic persons. Whether the affected individuals are peculiar in one or another respect or may only exhibit a more advanced state of a general tendency is not clear. It is probable that mild degrees of decalcification or other osteopathies are seldom recognized.

Droese [25] pointed out the confusion in the literature on the classification of the osteopathies associated with undernutrition but believed that hunger osteoporosis can be distinguished from hunger osteomalacia and late rickets. At the end of World War I a wide variety of osseous disorders were described from Central and Eastern Europe,[26] including delayed ossification in young women [26a] and multiple spontaneous fractures.[27] All ages were represented, but the incidence was perhaps highest in elderly women.

In World War II osteopathies again were noted in Europe, the most frequently observed form being that in which there are areas of translucency in the cortex of the long bones and spontaneous fractures at points of mechanical strain.[28] Pompen and associates [28b] described 24 cases of what they called "hunger osteopathy." They stated that in all cases the diet had been deficient in calcium, phosphorus, protein and vitamin D, and many of the patients had been indoors for long periods. Though undernourished, these patients were not really starved. This situation is radically different from that of the American prisoners of war in Japanese prison camps who showed roentgenologic evidence of osteoporosis on repatriation; these persons had ample exposure to the sun and frequently ate ground fish bones in prison.[29] Such evidence does not support a belief that either calcium or vitamin D deficiency is essential to the development of hunger osteopathy.

In the Minnesota experiment bone density was studied by Dr. Pauline Berry Mack with elaborate quantitative methods developed at Pennsylvania State College. Evidence of any abnormality in bone density was not seen. It seems probable that hunger osteopathies tend to develop only when the undernutrition is prolonged (for a year or more), and even then there must be other factors operative because the incidence never seems to be exceedingly high in famine populations.

13. MORPHOLOGY: MUSCULAR TISSUES

Muscular wasting is always a prominent feature of severe undernutrition. Experimental studies on animals indicate that, in general, the percentage weight loss of the voluntary muscles is somewhat greater than percentage weight loss of the entire body. Most of this wasting seems to be a result of shrinkage of the individual muscle fibers, but in late stages actual destruction of the cells may occur (Jackson,[6] page 162). Brown atrophy, loss of cross striations and granular degeneration have been described, as well as a reduction in the liposomes (minute fat droplets) and occasional appearance of vacuoles.

Presumably, moderate undernutrition only affects

23. Behnke, A. R., Jr.; Feen, B. G., and Welham, W. C.: The Specific Gravity of Healthy Men: Body Weight Divided by Volume as an Index of Obesity, J. A. M. A. 118:495-498 (Feb. 14) 1942. Rathbun, E. N., and Pace, N.: Studies on Body Composition: I. The Determination of Total Body Fat by Means of the Body Specific Gravity, J. Biol. Chem. 158:667-676, 1945. Morales, M. F.; Rathbun, E. N.; Smith, R. E., and Pace, N.: Studies on Body Composition: II. Theoretical Considerations Regarding the Major Body Tissue Components, with Suggestions for Application to Man, ibid. 158:677-684, 1945.

24. Laboratory of Physiological Hygiene, University of Minnesota, unpublished studies.

25. Droese, W.: Beitrag zur Frage der senilen Osteomalazie und der Hungerosteopathie, München. med. Wschnschr. 68:1199-1202, 1938.

26. (a) Boehme, A.: Gehauft auftretende Knochenerkrankungen infolge von Unternahrung, Deutsche med. Wchnschr. 45:1160-1162, 1919. (b) Stransky, K.: Roentgenbefunde bei alimentarer Skelettschädigung, Wien. klin. Wchnschr. 32:712-713, 1919.

27. Alwens: Ueber die Beziehungen der Unternahrung zur Osteoporose und Osteomalazie, Munchen. med. Wchnschr. 68:1071-1075, 1919. Boehme.[26]

28. (a) Burger, G. C. E.; Sandstead, H. R., and Drummond, J.: Starvation in Western Holland, Lancet 2:282-283, 1945. (b) Pompen, A. W. M.; La Chapelle, E. H.; Groen, J., and Mercx, K. P. M.: Hunger Osteomalacie in Nederland, Amsterdam, Wetenschappelijke Uitgeverij, 1946.

29. Hibbs, R. E.: Personal communication to the author.

the mass of sarcoplasm, at least for a time, and full recovery on refeeding should be possible. With more severe starvation, where muscle cells are undergoing actual destruction, it may be thought that full recovery could be brought about only by relative hypertrophy of the remaining intact muscle cells. However, mitoses in skeletal muscle of adult animals have been reported during ample feeding following starvation.[30]

Contrary to the textbooks, heart muscle behaves much like skeletal muscle in starvation. In both acute and chronic undernutrition the heart shrinks in volume and in weight, the loss being nearly in proportion to the total weight loss of the body.[31] In the Minnesota experiment the average gross volume of the heart, at systole, measured from teleroentgenkymograms, decreased 17 per cent when the body weight decreased 24 per cent. Since the starved heart may well eject its blood less completely than the normal heart, the actual tissue loss may be underestimated by this roentgenologic method, but in animals the weight loss of the heart is generally a trifle less than proportionate to the total weight loss.

The position of the heart in the chest is also changed in starvation so that ordinary linear measurements do not give an exact indication of the change in total size. In the Minnesota experiment the major axis of the heart in the standing position was, on the average, 4.4 degrees more vertical in starvation than in the control period.

14. MORPHOLOGY: BRAIN AND NERVOUS TISSUE

It has long been taught that the brain and the heart are somehow "protected" in starvation, so that they do not shrink and waste as do the other soft tissues of the body. In the case of the heart, as has been noted this view is in error. But all evidence is in agreement that the brain, and nervous tissue generally, loses little weight even in severe starvation. This does not necessarily mean, however, that these tissues are really unaffected by undernutrition. Histologic examination reveals atrophy, cloudy swelling, chromatolysis and a variety of degenerative changes in the cells.[32] The explanation of the apparent paradox may be suggested by the general agreement that vacuoles and evidences of edema appear in the nervous tissue. Presumably the weight changes are limited because the gross structure is preserved with replacement of cytoplasm, or even of cells, by water. The changes in the spinal cord are similar to those in the brain and may be even more pronounced in the anterior horn cells.[33] Nor are the peripheral nerves immune to the effects of starvation, though the medullated fibers are only slightly affected, morphologically.[9]

15. SKIN, HAIR AND EYES

Caloric deficiency of more than slight degree tends to produce characteristic changes in the skin and hair, but these are not specifically pathognomonic. The skin becomes thin, dry, scaly, inelastic, pallid and grayish. It is cold and "dead" to the touch and tends to slight cyanosis in cold weather. The appearance suggests old age. Besides these changes, which are generally seen and were striking in the men in the Minnesota experiment, there are other changes which appear with less regularity.

A substantial proportion of persons subsisting on a European type of famine diet exhibit rough gooseflesh-like areas of skin, most often on the extensor surfaces of the thighs and upper arms. The condition resembles the follicular hyperkeratitis and folliculosis sometimes associated with vitamin A deficiency. The causation is puzzling because its incidence is highly variable and does not seem to be clearly related to the state of vitamin A nutrition.[34] This condition did not appear in the inmates of Japanese prison camps in spite of gross dietary deficiencies.[9a]

A remarkable peculiarity of the skin in starvation has escaped serious attention until recently. A splotchy, dirty brownish pigmentation, appearing anywhere on the body but most often seen on the face, was casually mentioned in some old reports on undernutrition but occasioned much surprise when it was frequently seen at the close of World War II.[34a] Most of the Minnesota men exhibited it to some degree. The mechanism of the production of this famine pigmentation is unknown; it is not related to nicotinic acid deficiency or pellagra.

The hair in starvation is usually dry, dull and staring. There are many impressions that hair almost ceases to grow and tends to fall out, but objective evidence is lacking.

There is a characteristic appearance of the eyes in starved persons. They look dull and dead. On closer inspection it is seen that the sclera and cornea are unusually devoid of blood vessels so that the whites of the eyes resemble unglazed procelain. In the Minnesota experiment men even soap solution failed to produce reddening.

16. MORPHOLOGY: BLOOD VOLUME

With the exception of bone and nervous tissues, the formed tissues of the body generally are decidedly diminished in gross bulk in undernutrition. In some respects it is proper to consider the blood as a tissue, and its behavior in comparison with other tissues is of interest. More particularly, it is essential to allow for changes in the gross mass of the blood before evaluating the true meaning of changes in the concentration of the formed elements.

Measurements of the blood volume in relation to the nutritional state are still few in number, and some limitations in the technical methods restrict the conclusions which may be drawn from the data. All present methods refer only to the circulating blood. Although in man the reservoirs of noncirculating blood are small, it is possible that the situation may not be precisely the same in normal and in starved persons. Moreover, when starved and normal persons are compared there is the question as to how the blood volume should be expressed to allow properly for differences in gross body size.

Plasma volume was estimated in 15 inmates of the Belsen concentration camp who had lost something like 30 or 35 per cent of their body weight.[35] In the Minnesota experiment the plasma volume was studied systematically before, during and after starvation.[36] As far as they go, the Belsen data confirm the Minnesota work. Before starvation the Minnesota subjects had an average plasma volume of 3.15 liters, and this amounted to 45.3 cc. per kilogram of body weight. At the end of six months of semistarvation the absolute

30. Jackson,[9] p. 167.
31. Keys, A.; Henschel, A., and Taylor, H. L.: The Size and Function of the Human Heart at Rest in Semi-Starvation and in Subsequent Rehabilitation, Am. J. Physiol. 150: 153-160, 1947.
32. Jackson,[9] p. 181.
33. Jackson,[9] p. 195.
34. Robinson, W. D.; Jannery, J. H., and Grande, F. C.: An Evaluation of the Nutritional Status of a Population Group in Madrid, Spain, During the Summer of 1941, J. Nutrition 24: 557-584, 1942.
35. Mollison, P. L.: Observation on Cases of Starvation at Belsen, Brit. J. 1: 4-8, 1946.
36. Henschel, A.; Mickelsen, O.; Taylor, H. L., and Keys, A.: Plasma Volume and Thiocyanate Space in Famine and Recovery, Am. J. Physiol. 150: 170-180, 1947.

plasma volume had increased slightly to an average of 3.41 liters, but this then represented 59.3 cc. per kilogram of the total body weight.

The absolute plasma volume, then, tends to remain constant or increases slightly in starvation. The associated anemia means that the total circulating blood volume is somewhat reduced, but in proportion to the body weight there is a definite blood plethora. These changes are slowly reversed in subsequent rehabilitation; the Minnesota men were fully restored in this respect in about three months.

The behavior of the blood volume in the terminal stages of the most severe starvation may be more complex. Some famine victims die in obvious shock with all signs of severe dehydration; the persistent diarrhea often seen in these cases may produce dehydration, sharp reduction in blood volume and shock as in cholera.

17. MORPHOLOGY: BLOOD CELLS

Some degree of anemia is invariably observed in persons who have undergone prolonged semistarvation. In Asia severe anemia is frequently seen in such persons, but this is probably mainly a reflection of the effect of malaria and other blood-destructive conditions.

In the Minnesota experiment the diet, like European famine diets, was not deficient in iron but there was a progressive moderate anemia in every man during semistarvation. Beginning with an average of 15.1 ± 0.88 Gm. per hundred cubic centimeters of blood in the control period, the average value declined to 12.6 ± 0.80 Gm. after 12 weeks of semistarvation (15 per cent weight loss) and to 11.7 ± 0.80 Gm. at 24 weeks when the weight loss was 24 per cent.[36] These changes are comparable to many observations in famine areas in Europe.

In general, the erythrocyte count and the hematocrit reading change as does the hemoglobin concentration, but the parallelism is not exact. The red blood cells tend to become slightly larger in starvation; the anemia is of the macrocytic type. In the Minnesota experiment the average volume of the red cell, and the content of hemoglobin in it, had increased about 7 per cent at the end of semistarvation.

From the data on plasma volume, the hematocrit reading and the hemoglobin concentration, the total circulating hemoglobin can be calculated. In starvation this is decreased, the decrease in the Minnesota experiment being almost exactly in proportion to the decrease in gross body weight.[36]

The cause of the anemia in undernutrition is not clear; iron deficiency is not primarily responsible. Sternal marrow examinations so far have not provided the answer. Increased, decreased and normal degrees of erythropoiesis have been found in the marrows of anemic starving persons. The possibility that excessive peripheral destruction of the red blood cells is involved is suggested by reports of hemosiderin deposits in the tissue.[37]

In comparison with the rather large variability of leukocytes in normal subjects, the changes in starvation are ordinarily not dramatic. A definite but moderate leukopenia is the rule except where there is intercurrent infection. In the Minnesota experiment the mean leukocyte count was 6,346 per cubic millimeter in the control period and at the end of semistarvation it was 4,129, a decline of 34.9 per cent (see also Zimmer [38]). Correcting for the change in total blood volume, the decrease in total circulating leukocytes averaged 24.1 per cent.

The composition of the leukocytes by types in semistarvation and in fasting has been reported many times in the older literature, but no consistent picture emerges. Several workers found an apparent relative lymphocytosis,[38] but this was not observed in the Minnesota experiment.

In rehabilitation following prolonged undernutrition the correction of the anemia takes place slowly even when protein and iron are supplied in abundance. In the Minnesota experiment the hemoglobin concentration only recovered slightly in 12 weeks and was still appreciably below the control values at 20 weeks when the body weight had been regained; 3 months later, however, (i.e., a total of 8 months after the end of semistarvation), the blood was normal.

18. THE GASTROINTESTINAL TRACT

Gastrointestinal disorders are almost invariably reported from famine areas and frequently contribute greatly to the disability and death of famine victims. Diarrhea and dysentery are always major factors in famine mortality in India,[39] and were prevalent in Europe in both World Wars.[40] The majority of internees and prisoners of war in the Japanese camps in World War II suffered from diarrhea.[39a] In such situations, however, there is a breakdown of sanitation or recourse to strange and peculiar materials as food, or both, so that it is impossible to assess the effects of undernutrition as such.

Attempts to isolate specific pathogens from the stools in most of these cases have been conspicuously unsuccessful. If organisms in the intestine are responsible it must be concluded that forms which normally are not pathogenic may interfere with the function of the intestine of the starving man. Famine victims usually eat anything and everything they can get, and this often means the consumption of irritating, indigestible and spoiled foods, so that nonspecific diarrhea would not be surprising except for its severity.

In the Minnesota experiment, in which strict sanitation was maintained and bad or questionable items of food were never used, diarrhea did not occur at any time though the degree of starvation was comparable to that in the field where diarrhea is so pronounced. This would seem to prove that starvation alone is not causative.

Extreme pathologic changes are often found in the intestinal mucosa of famine victims. These changes may explain the diarrhea in a sense, but the tissue changes are probably the resultant of several factors, of which caloric undernutrition is only one. Certainly starvation produces degenerative changes in all the tissues of the gastrointestinal tract as elsewhere in the body. Additional insult may then easily produce a variety of disorders. An increase in peptic ulcer is commonly noted in periods of undernutrition.[41]

The course of the digestion as affected by starvation is an important question in devising relief programs. In the spring of 1945 it was at first thought that many

37. Lubarsch, cited by Luisada, A.: Beitrag zur Pathogenese und Therapie des Lungenödems und des Asthma cardiale, Arch. f. exper. Path. u. Pharmakol. **139**: 313-329, 1928.

38. Bigland, A. D.: Oedema as a Symptom in So-Called Deficiency Diseases, Lancet **1**: 243-247, 1920. Benedict, Miles, Roth and Smith.[3]

39. Aykroyd, W. R.: Nutrition and Health, Indian M. Rec. **59**: 113-116, 1939. Porter.[8]

40. Debray, C.; Zaracovitch, M.; Ranson, B.; Jacquemin, J.; Robert, G., and Straga, M.: Contribution a l'étude de la pathologie des déportés, Semaine d. hôp. de Paris **22**: 863-870, 1946. Brozek, Wells and Keys.[33] Burger, Sandstead and Drummond.[39a]

41. Magee, H. E.: Application of Nutrition to Public Health: Some Lessons of the War, Brit. M. J. **1**: 475-486, 1946.

famine victims in Europe would require intravenous alimentation, but this proved undesirable in trials in the Netherlands and later in the Belsen concentration camp. Frequent feedings of easily digested foods usually bring about rapid improvement; when this is not the case even the most careful intravenous management may be unsuccessful. The critical point may be indicated by dysphagia. If the patient still feels the pangs of hunger and wants to eat, even a rough and ready feeding program with plain foods will suffice; if the appetite is gone the prognosis is bad (except in anorexia nervosa).

In the Minnesota experiment there were few indications of digestive impairment and no complaints on this score. Gastric acidity (fasting and after histamine) was substantially normal. Gastric motility (rate of evacuation of a test meal) was slightly but consistently depressed.

19. THE BASAL METABOLIC RATE

The basal metabolic rate always represents a large fraction of the total metabolism so that its relation to the caloric intake is a major determinant in the caloric balance. Under normal conditions the basal metabolic rate of the individual is relatively fixed and differences between persons of the same age and sex are considered to be dependent on body size and on the activity of the thyroid gland. It is generally believed that habitual differences in food intake and relative obesity in normal persons have little or no effect on the basal metabolic rate. Persons who are habitually thin, even to a decided degree, apparently have a normal basal metabolic rate when this is expressed per unit of body surface.[42]

When the food intake is sharply reduced below the habitual level for the subject the basal oxygen consumption promptly declines, and this alteration tends to be progressive if the inadequate diet is continued; the absolute change is large. The 32 men in the Minnesota experiment had an average basal consumption of 229 cc. per minute before starvation. After 12 weeks of the famine diet, when the body weight had fallen 15 per cent, this had decreased to 155 cc. and after 24 weeks the average was 139 cc. per minute; a loss of 24 per cent in body weight was associated with a drop of 39 per cent in the basal oxygen consumption. These data, which extend and confirm earlier results, are of obvious practical significance. When subsistence is maintained at a calorically deficient level the progress of the undernutrition itself progressively decreases the caloric deficit so that there is a tendency toward adaptation or compensation.

The absolute changes in the basal metabolism raise questions about the mechanisms involved and the intensity and character of the metabolic processes in the metabolizing tissues. These changes are not merely a reflection of changes in the body surface which would be predicted from the so-called surface law. In the Minnesota experiment, for example, there was an average drop of 28 per cent in the oxygen consumption per square meter of body surface. Subnormal values for the basal metabolic rate, expressed in units of body surface, are universally found in famine areas.

Analysis of these data suggests the need for renewed scrutiny of the surface law. As the body shrinks in starvation the surface increases relative to the tissue mass so that, other things being equal, there would be a greater heat loss and a lower point of temperature equilibrium. The lowered body temperature in turn would retard the enzymatic processes which constitute the metabolism. Although such a chain of events undoubtedly operates, it is not possible to explain the total metabolic alterations on this basis. The decline in body temperature is exceedingly small; in the Minnesota experiment it fell less than 1 degree (F.) in 24 weeks. As a matter of fact, the theory of a heat exchange basis for the surface law is no longer seriously entertained. Changes in peripheral blood circulation readily control the body temperature in the face of great changes in heat production and external temperature.

An important problem is the behavior of the metabolic rate per unit of metabolizing tissue. A first approximation is obtained by expressing the metabolic rate in relation to gross body weight. In the Minnesota experiment the basal oxygen consumption per kilogram of body weight declined 15 per cent in semistarvation. But the gross body weight is not necessarily a reliable index of metabolizing tissue. Fat, bone mineral and extracellular water clearly have little or no metabolic activity. In starvation the proportional composition of the body is changed, there being a relative reduction in fat and relative increases in bone mineral and extracellular water. When allowance is made for these differences, which is possible with the Minnesota data, the apparent alteration in metabolic intensity is reduced but the values are still about 10 per cent below the prestarvation control. In other words, prolonged severe undernutrition produces a small but seemingly significant drop in the basal metabolic rate per unit weight of active tissue (body weight less weights of fat, bone mineral and extracellular water).

In rehabilitation following undernutrition the basal metabolic rate rises more or less parallel to the dietary intake and the gain in body weight. Before body weight is fully restored, however, and for some weeks or months thereafter, the basal metabolic rate surpasses the value which was characteristic of the subject in the prestarvation state. This is particularly clear when the basal metabolic rate is expressed per unit of active tissue or per unit of body weight less fat. In the latter terms the average for the men in the Minnesota experiment after 20 weeks of refeeding, when body weight had been restored, was 13 per cent above their own normal metabolic rates.

20. TOTAL ENERGY METABOLISM

The total energy metabolism is made up of the basal metabolic rate, the specific dynamic action (some 10 per cent of the basal metabolic rate), and the cost of muscular movement and tonus in excess of the basal state. In starvation or severe undernutrition the basal metabolic rate is sharply diminished, as previously noted. Presumably there is also a proportional reduction in the specific dynamic action. The other items in the total metabolic picture are also much reduced.

The energetic efficiency of muscular activity is substantially unaltered in undernutrition except in the most extreme states where gross incoordination may interfere. The energy cost per kilogrammeter of external work like walking and bicycle riding is practically unaltered. This simplifies the analysis.

A large part of the energy cost of muscular work is entailed by moving the body or its parts. In locomotion the work done is simply proportional to the body weight. It follows, then, that the metabolic cost of muscular work is reduced in starvation because of the

42. Blunt, K.; Nelson, A., and Olesen, H. C.: The Basal Metabolism of Underweight Children, J. Biol. Chem. 48:247-262, 1921. Strang, J. M.; McCluggage, H. B., and Brownlee, M. A.: Metabolism in Undernutrition: Its Changes During Treatment by High Calorie Diet, Arch. Int. Med. 55:958-978 (June) 1935.

reduction in weight of the body and its movable parts. For the majority of activities the reduction in work energy may be considered roughly proportional to the loss in body weight.

Perhaps even more important in most natural life situations is the fact that voluntary activity is greatly diminished in severe undernutrition. Energy expenditure is automatically curtailed and the starving man tends to be immobile, to move slowly when movement is necessary and to assume postures which are most conservative of energy.

The combined effect of all these factors is a large reduction in energy expenditure. In the Minnesota experiment the daily total energy expenditure at the end of semistarvation was only about half that in the control period, in spite of the fact that a fixed occupational and exercise program was maintained throughout. In severe natural famine the reduction in energy expenditure may be considerably greater, so that caloric balance may be achieved at surprisingly low figures. The caloric deficit is apt to be grossly overestimated when calculated simply from caloric intakes.

During nutritional rehabilitation the return of a sense of well-being is coupled with an increase in voluntary physical activity, but the habit of energy conservation is not quickly broken. An effort of will or coercion is often necessary to promote recovery in physical fitness by exercise. The total daily metabolism tends to lag behind the proportional change in the basal metabolic rate in recovery.

21. THE CARDIOVASCULAR SYSTEM

The response of the cardiac musculature to undernutrition has been mentioned in section 13. Changes in cardiac and circulatory function are obvious and in some respects more dramatic.[43] It is well known that both total fasting and prolonged undernutrition tend to produce bradycardia and hypotension in rest. The significance of these changes and other details of circulatory function have received little attention until recently.

Starvation bradycardia is obvious in all instances except where there are extremely powerful heart-accelerating forces at work, such as systemic infection, great excitement or fear, or impending circulatory collapse. From the literature the impression is gained that the bradycardia is perhaps most profound in the earlier stages of severe undernutrition; certainly the degree of bradycardia is not simply related to weight loss. This was also indicated in the Minnesota experiment where the subjects' average basal pulse rate of 34.9 per minute after 12 weeks rose to 37.8 after 24 weeks of semistarvation.

The contrast with beri-beri heart is important. In beri-beri, there may be resting bradycardia but small physical exertion produces decided tachycardia. In simple starvation, exercise produces an increase in the heart rate but this is not disproportionate to the resting rate.

The bradycardia of starvation does not involve heart block; the rhythm is of the sinus type.[43] The rhythm is remarkable for its great regularity; the variability of the length of the P-R interval is smaller than normal in both absolute and relative terms. The electrocardiogram in a state of severe undernutrition shows peculiarities in almost every item of measurement,[43b] but the amplitude changes are most striking. The voltages of all deflections are reduced, particularly the P waves and the QRS complex.

Both systolic and diastolic blood pressures are reduced by undernutrition but these changes, unlike the bradycardia, are moderate and progressive. In severe chronic undernutrition the systolic blood pressure is generally reduced 10 to 30 mm., with a smaller drop in diastolic pressure; the pulse pressure is invariably narrower.[21] These changes have interesting relations to problems of hypertension.[44]

The total circulatory function in starvation is, superficially at least, well preserved. Though there is a tendency to slight peripheral cyanosis, there are usually no complaints referred to the heart and no signs of impending or actual failure except in the terminal state. Nevertheless, detailed analysis indicates that the margin of safety is reduced and that the rate of circulation per unit of metabolic rate is substantially lowered.[21]

In starvation it is common to observe fainting and giddiness, particularly in the upright posture. It is surprising, therefore, to note that no inadequacy of circulatory adjustment to posture is revealed by tilt-table tests.[45]

The restoration of cardiocirculatory function to normal by refeeding does not necessarily follow a simple path of reversal of the starvation changes. When the rehabilitation diet is abundant there may appear signs of relative cardiac insufficiency at the time when the rate of gain of weight and of the basal metabolic rate are at their peaks. The pulse rate, in both rest and exercise, and the venous pressure tend to exceed normal control values, and even frank congestive failure may intervene.[21] The sudden rise in the basal metabolic rate in rehabilitation may produce an intolerable strain on the heart. Full restoration of the heart is not as readily achieved as is the body weight.

22. STRENGTH AND COORDINATION

All psychomotor functions deteriorate in caloric deficiency, and the result is a serious impairment in working capacity. Simple muscular strength, as measured in a single maximal exertion, declines steadily but not as dramatically as does the capacity for continued muscular exertions (endurance). In the Minnesota experiment the single-effort strength of hands, arms and back declined about 30 per cent and the endurance in severe work which produces exhaustion in a few minutes fell as much as 85 per cent. Collapse in the latter tests appeared to be due to muscular failure instead of the circulatory-respiratory type seen in normal persons.

Neuromuscular coordination is impaired by caloric undernutrition, but the relative deterioration is less than in purely muscular capacity.

The psychomotor functions are only slowly restored by refeeding. When the body weight has been regained, there may still persist a serious reduction in muscular endurance. In young men full recovery in these respects takes the better part of a year.

23. THE SPECIAL SENSES

Simple caloric starvation seems to have no deleterious effects on the special senses. In the Minnesota experiment visual acuity was unaffected and there was no evidence of alteration in the senses of touch, taste and smell. Auditory acuity is ordinarily slightly improved

43. (a) Cardoso, E. L., and Egnish, P.: Circulation Failure in Hunger Edema, Canad. M. A. J. 54:145-147, 1946. (b) Simonson, E.; Henschel, A., and Keys, A.: The Electrocardiogram of Man in Semi-Starvation and Subsequent Rehabilitation, Am. Heart J., 35:584-602, 1948.

44. Brozek, J.; Chapman, C. B., and Keys, A.: The Effect of Semi-starvation on Cardiovascular Dynamics in Normotensive and Hypertensive Persons, J. A. M. A., to be published.

45. Taylor, H. L.; Henschel, A., and Keys, A.: The Cardiovascular Response to Posture and the Problem of Faintness and Syncope in the Semi-Starved Individual, Am. J. Physiol. 152:141-149, 1948.

at all frequencies; this was clearly demonstrated in the Minnesota subjects and is confirmed by less objective methods from famine areas. The cause of the sharpened hearing may be mechanical, associated with an enlargement of the free space in the auditory canal. The improvement in hearing is lost during nutritional rehabilitation.

24. INTELLECTIVE FUNCTIONS

Starving persons are ordinarily averse to any effort, including that of the intellect, and their preoccupation with food and their own plight may give an impression of stupidity or mental incapacity. Actually, however, there is no evidence for a decline in basic intellective capacity. In the Minnesota experiment exhaustive studies on memory, reasoning power, verbal and arithmetical facility, and so on, revealed no changes in spite of the subjective impression of most of the men that their mental powers had been reduced.

25. PERSONALITY AND EMOTION

Severe caloric inadequacy produces profound changes in the personality and the subjective state.[46] Externally, the major characteristics are apathy, depression and introversion. Social contacts are avoided and sex interest declines sharply. Psychiatric methods reveal, besides the depression, a well defined rise in the tendencies to hypochondriasis and hysteria. Though the behavior is almost never aggressive, it is easy to discern a tendency to a heightened irritability. The behavior which would ordinarily be associated with increased irritability is suppressed by the overwhelming physical lethargy.

It is difficult to appreciate the enormous preoccupation of the starving man with food and eating. His thoughts tend to be exclusively dominated with these concerns. Their expression may range from constant day-dreaming about eating to extensions such as interest in scientific agriculture. Niceties of behavior are brushed aside where they interfere with the full expression of these interests. Even when the food supply is restored the concern about food persists for many months; a common expression is food hoarding, even when there is not the slightest reasonable basis for this.

Emotional crises and seriously disturbed behavior may arise from the conflict between the concentration on food and previously fixed convictions.[46b] While these may result in irritated or antisocial behavior or even lead to self-destructive impulses, they do not partake of the character of the true psychoses.

Personality changes in refeeding may be even more complex; certainly the behavior may be more variable. As the physical state improves the tendencies toward depression and hypochondriasis diminish, but they may be returned in force by disappointment in the rate of recovery or threats of renewed food restrictions. The return of physical vigor allows outward manifestation of formerly suppressed irritability. At this stage these persons are far more difficult to manage and maintain in an orderly social structure than when they were physically deteriorating. These facts obviously have great sociologic importance.

26. UNDERNUTRITION AND RESISTANCE TO INFECTION

There is no aspect of undernutrition about which there is a more fixed common belief—and less objective evidence—than the question of the effect on resistance to infection. The historical association of famine and pestilence has been so uncritically accepted as indicating cause and effect that there is a dearth of actual research and analysis. The whole problem of nutrition and infection is enormously complicated;[47] obviously no broad generalizations are possible.

Properly, each infectious disease should be considered separately. However, only in the case of tuberculosis is there an appreciable amount of acceptable information. Tuberculosis is discussed separately (section 27); here the other problems are noted briefly. The evidence, such as it is, concerns: (1) indirect suggestions from antibody titers, precipitins, gamma globulin and the like; (2) animal experiments involving experimental infection; (3) casual observations on natural infections in animals; (4) clinical reports, and (5) morbidity and mortality data from famine areas.

A long series of papers from Dr. Paul Cannon's laboratory has stressed the importance of nutrition, particularly protein nutrition, in antibody formation.[48] Most of these animal experiments involved both severe caloric and protein deficiencies, the latter being more drastic than usually seen even in severe famine. The exact relevance of these observations to human caloric deficiency is uncertain; the data themselves are contrary to some older studies.[49]

Experimental studies with injections of micro-organisms into animals in various states of nutrition have been few and of indifferent quality. Opposing observations make it clear that no general conclusions are possible so far (e.g., Edwards[50] versus Robertson and Tisdall[51]). Reports on the incidence and course of natural infections in underfed animals are similarly at variance.[52]

Clinical records may be used to support or to oppose the claim that caloric deficiency, per se, produces a decreased resistance to infection. Some interesting recent data have to do with clinical experience in hospitals associated with prison camps in World War II where surgical procedures were often performed on persons in a deplorable nutritional state without unusual complications.[53]

Morbidity and mortality records from World War II provide material for thought. In contradistinction to previous wars, pestilence was never rampant except where sanitation control was neglected. No epidemics appeared in Western Holland or Greece at the times when there was mass starvation in those areas. The diphtheria epidemic of 1946 appeared to affect the American occupation troops just as severely as the underfed populace. Markowski[54] stated that typhus mortality was worse among the German guards than among the starving Russian prisoners at Hammerstein.

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46. (a) Franklin, J. C.; Schiele, B. C.; Brozek, J., and Keys, A.: Observations on Human Behavior in Experimental Semi-Starvation and Rehabilitation, J. Clin. Psychol. 4: 28-45, 1948. (b) Schiele, B. C., and Brozek, J.: Experimental Neurosis Resulting from Semi-Starvation in Man, Psychosom. Med., 10: 31-50, 1948.

47. Schneider, H. A.: Nutrition and Infection, the Strategic Situation, in Harris, R. W., and Thimann, K. V.: Vitamins and Hormones, New York, Academic Press, Inc., 1946, vol. 4, pp. 35-70.

48. Cannon, P. R.; Winsler, R. W.; Woolridge, R. L., and Benditt, E. P.: The Relationship of Protein Deficiency to Surgical Infection, Ann. Surg. 120: 514-525, 1944. Cannon, P. R.: The Importance of Proteins in Resistance to Infection, J. A. M. A. 128: 360-362 (June 2) 1945; The Relationship of Protein Metabolism to Antibody Production and Resistance to Infection, in Anson, M. L., and Edsall, J. T.: Advances in Protein Chemistry, New York, Academic Press, Inc., 1946, pp. 135-154.

49. Zilva, S. S.: The Influence of Deficient Nutrition on the Production of Agglutinins, Complement and Amboceptor, Biochem. J. 13: 173-194, 1919.

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52. McCay, C. M.: Nutrition, Ageing and Longevity, Tr. & Stud., Coll. Physicians Philadelphia, 10: 1-10, 1942.

53. Gotzlieb, M. L.: Impressions of a POW Medical Officer in a Japanese Concentration Camp, U. S. Nav. M. Bull. 46: 663-673, 1946.

54. Markowski, B.: Some Experiences of a Medical Prisoner of War, Brit. M. J. 2: 361-363, 1945.

On the whole, the evidence to date suggests that there are various relations in different animals and with different organisms, that the old association of famine and pestilence was largely due to sanitary faults and that in man caloric deficiency is not necessarily productive of a lowered resistance or a heightened susceptibility to infectious diseases in general.

27. TUBERCULOSIS

As far into the past as there are records it is clear that tuberculosis has always increased in periods of severe food restriction. The evidence for the period of the first World War is particularly valuable because it is possible in some cases to dissociate the factor of food shortage from those of overcrowding, excessive labor, sanitation and medical care. The data from Germany [55] are useful, but the analysis of Faber [56] for the situation in Denmark is most significant.

Denmark's domestic food consumption in World War I decreased and then increased owing to the blockade. The housing situation became extremely bad after the food supply was maintained at a good level. Medical care was well maintained at all times. Sharp changes in tuberculosis mortality were closely related to the level of food consumption and were relatively independent of overcrowding, unemployment and the like.

The data from World War II are adding much confirmation to the conclusion that tuberculosis morbidity and mortality are increased by caloric deficiency.[57] In some cases changes in ascertainment distort the figures,[41] but the general picture is convincing. Clinical reports from areas of food shortages emphasize the frequency of a fulminating type of the disease. Tuberculosis is certainly a most serious problem under any circumstance when there is a prolonged severe food shortage.

28. UNDERNUTRITION AND NEOPLASTIC DISEASES

It is now well known that the incidence, growth and recurrence of several types of tumors in animals can be reduced or even prevented by exceedingly severe undernutrition.[58] The prophylactic and therapeutic possibilities of caloric restriction in man have been argued,[59] but there are serious difficulties in application. In animal experiments inhibition of tumors has required the use of dietary levels so low as to retard growth greatly and to prevent estrus.[60] While such levels are reached in human famine, there are no data to show any important effect on the incidence or course of cancer in man. The most that may be said is that the mortality statistics from starvation periods (e.g., in Greece and the Netherlands) do not indicate any increase in cancer; the number of deaths ascribed to neoplasms is reduced in proportion to the total deaths.[11]

29. HYPERTENSION AND CORONARY DISEASE

It has been noted (section 21) that caloric undernutrition normally produces a fall in the blood pressure. What effect this may have on the incidence and course of hypertension and vascular diseases in general is an intriguing question. There are many clinical impressions which are suggestive, but these have little objective basis. Mortality data from famine areas are of limited value because of the problems of certification; in most cases the figures are only grouped under such broad headings as "cardiovascular disease."

The hospital records of Leningrad during the siege of 1941-1942 and after are interesting. In this period of severe food shortage the hospital admissions for hypertension remained at about the ordinary level but the deaths from such conditions dropped sharply.[61] After the food supply was restored to much better levels there was a veritable epidemic of hypertension and coronary deaths in Leningrad. Transient hypertension during refeeding was also noted in the Far East.[61] There is clearly an important area for research here.

30. UNDERNUTRITION AND DIABETES

The association of diabetes with obesity and the advantage of food restriction in this disease are well established.[62] These general relations are reflected in substantial changes in morbidity and mortality from diabetes during periods of food shortages even when these are not productive of real starvation.[63] An improvement in the clinical condition of patients with established diabetes is quickly apparent when the food supply is restricted. Beckert [64] compared 604 diabetic persons in Dresden in the summer of 1939 and again in the summer of 1940. A loss in weight was recorded in 62.2 per cent. Clinically, 45 per cent were improved and only 5 per cent were worse. In Belgium, moderate food shortages in the first three years of World War II were associated with a notable diminution in diabetes morbidity and a more favorable clinical course of this disease.[65]

31. FAMINE EDEMA

Famine (hunger or war) edema was in a sense "discovered" in World War I, though it had been casually observed throughout the ages. The simulation of this condition by protein depletion and a variety of evidences supporting Starling's theory of the role of colloid osmotic pressure in fluid balance led to almost universal belief, in spite of unheeded objections,[66] that famine edema is simply a result of hypoproteinemia. World War II, however, contributed an unexpected denouement.[67]

In starved persons edema may appear with relatively normal values for plasma protein concentration and the albumin fraction is not necessarily decreased. Furthermore, though on the average there may be some relation between the plasma protein level and the extent of the edema, the relation is extremely rough and does not hold for individuals.[68] Cardiac failure is not involved, and the venous blood pressure is actually lower than normal. Finally, it should be noted that the edema fluid is extraordinarily low in protein.

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68. Denz, F. A.: Hunger Oedema, Quart. J. Med. **10**: 1-19, 1947. Keys, Taylor, Mickelsen and Henschel.[67]

In ordinary cases of edema due to famine the edema is not so much an accumulation of tissue fluid as simply a retention of the prestarvation level of extracellular fluid; the edema tends to be the expression of a relative and not an absolute excess of fluid in the body. It is probable that mechanical factors—elasticity and structure—outside the capillaries are responsible.

The edema is ordinarily only moderate and is of the soft, dependent type, being notable in the face in the morning and shifting to the lower extremities during the day. Ascites is seldom seen except where there is severe anemia, intercurrent infection, heart failure or decided hypoproteinemia. The latter appears when the diet is unusually devoid of protein. The edema itself is not particularly troublesome, but it is a useful rough guide in evaluating the nutritional state in surveys; it is not a reliable or sensitive indicator in the individual. During refeeding it tends to appear and disappear, being affected by exercise and posture as well as the dietary level.

32. PROBLEMS OF REHABILITATION

The problems of nutritional rehabilitation following semistarvation periodically arise in acute form. The practical necessities of relief allow scant opportunity for research, and the factual information is extremely little. In large scale relief operations the limitations of food materials emphasize the distinction between optimal and feasible programs; the criteria must be those of efficiency and economy.

The character of the diet in the preceding period of semistarvation is important. In general, there are vitamin deficiencies to be corrected in Asia whereas in Europe these tend to be much less prominent. The severity of the state of undernutrition is a determining factor. Almost any food items may be used for the majority of an underfed population, but those persons in an extremely depleted state need easily digested food in frequent feedings. Intravenous feeding is seldom desirable or necessary.

Experience in Europe supports the observations in the Minnesota experiment where it appeared that calories in relative abundance are the first need. The Minnesota subjects manifested a rate of recovery closely proportional to the calories supplied; at intakes of less than 2,700 Calories daily, recovery was exceedingly slow and apparently would have required more than a year. In the Minnesota experiment it was found that intakes over 5,000 Calories daily are unnecessary and may be dangerous. In these young men engaged in light activity the optimal level appeared to be something like 3,500 Calories.

With adequate calories supplied in ordinary foods, including breads made with low-extraction flour, the protein intake will normally be 70 Gm. or more per day. At these levels the isocaloric substitution of protein for carbohydrate produced no discernible benefit in the Minnesota experiment. The extra protein supplement was limited to only 20 Gm. a day, but there is no reason to believe that larger amounts would have important effects.

Special vitamin supplements had no effect on the course of rehabilitation in the Minnesota experiment, nor is there any objective evidence of value in the trials in Europe. It is unnecessary to supply vitamin concentrates unless there is clinical evidence of vitamin deficiency and the relief diet itself is a poor source of vitamins.

With the best of diets and rehabilitation treatment, full recovery from severe undernutrition is slow. Body weight is regained long before functional normality is restored. When the undernutrition lasts for many months and the weight loss is between 20 and 30 per cent, it is probable that complete rehabilitation, including restoration of working capacity, is seldom achieved in less than a year in young adults. With older persons a slower recovery must be expected. It is possible that children recover more promptly.

33. LESSONS FROM CONTEMPORARY FAMINE EXPERIENCE

Acute and persistent problems of starvation and food shortages began to be apparent early in World War II. The problems were not new, but their overwhelming nature has focused attention on them so that it should no longer be possible for them to be neglected by nutritionists in favor of the spectacular advances concerning individual nutrients. But this reawakened interest is coming late, so late that years of opportunity for definitive research have been lost. The data gathered in and immediately after World War II are valuable, but they barely touch many points and on others leave confusion and uncertainty.

Many of the accomplishments and the problems recognized but unanswered are indicated in several recent discussions and monographs.[69] These may be examined with profit not only for the facts presented but for the indications of facts not collected, the theories not critically examined and the questions not answered.

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69 Drummond, J.: Famine Conditions and Malnutrition in Western Europe, J. Roy. Soc. Arts 94:170-177, 1946. Boerema, J.: Medische Ervaringen in Nederland Tijdens de Bezetting, 1940-1945, Groningen, J. B. Wolters, 1947. Elgwood, E. J.: Enseignements de la guerre 1939-1945 dans le domaine de la nutrition, Liege, Ed. Desoer, 1947. Fleisch.[70]

ACCEPTED FOOD

The following products have been accepted as conforming to the Rules of the Council.

JAMES R. WILSON, M.D., *Secretary.*

Vital Foods Corporation, Evanston, Ill. (Distributed by the American Hospital Supply Company, Evanston, Ill.)

TOMAC ORAL PROTEIN SUPPLEMENT, UNFLAVORED, consists of Ca-Sal (casein and lactalbumin), food yeast, lactalbumin, carrageenin and salt.

Analysis (submitted by manufacturer).—Protein (N × 6.25) 67.5%, carbohydrate 18.5%, ash 7.0%, moisture 6.0%, ether extractables 1.0%.

Calories.—3.25 per gram; 92 per ounce.

Use.—For conditions that require an increased intake of protein.

TOMAC ORAL PROTEIN SUPPLEMENT, FLAVORED, consists of Ca-Sal (casein and lactalbumin), lactalbumin, food yeast, sugar cane, carrageenin and flavor.

Flavoring.—Imitation powdered maple flavor, or pure lemon flavor with citric acid.

Analysis (submitted by manufacturer).—Protein (N × 6.25) 61.5%, carbohydrate 26.5%, ash 6.2%, moisture 5.1% and ether extractables 0.7%.

Calories.—3.25 per gram; 92 per ounce.

Use.—For conditions that require an increased intake of protein.

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Analysis (submitted by manufacturer).—Butterfat 28.40 per cent, protein (N × 6.38) 26.35 per cent, lactose 37.47 per cent, ash 5.78 per cent, moisture 2.00 per cent and 400 U.S.P. units of vitamin D_3 per reconstituted quart.

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SATURDAY, OCTOBER 16, 1948

BCG VACCINATION

Of the two methods of preventing tuberculosis, namely, segregation of infected persons and immunization of those exposed to infection, the latter, according to Birkhaug,[1] has not received sufficient emphasis in this country. The skeptical attitude toward immunization is reflected in the recent report of Levine and Sackett[2] on the results of BCG immunization in New York City. Those authors expressed the opinion that as a public health measure the routine vaccination of children from tuberculous homes is less advantageous than the removal of the tuberculous person from the home. While tuberculosis control programs, exclusive of vaccination, have reduced the death rate from tuberculosis in the United States from 200 to 36 per 100,000 population in the last forty years, Denmark, during the same period, utilizing both segregation and immunization, has reduced tuberculosis mortality from about 300 to 32 per 100,000 population. Holm[3] stated that since 1940 vaccination with the bacillus Calmette-Guérin has been adopted in Denmark as an essential weapon in the fight against tuberculosis. All children with a negative tuberculin reaction in a tuberculous environment have been vaccinated, also the newborn, and on development of a positive reaction they have been permitted to remain in their environment. The Tuberculosis Dispensary of Copenhagen reported that morbidity and mortality of tuberculosis among the children in a tuberculous environment has been reduced following vaccination to almost zero. Holm expressed the belief that BCG vaccination gives considerable, although not absolute, protection. It protects almost completely against the morbid phenomena of the primary infection, and it also affords considerable protection against genuine tuberculosis of the various organs, in particular against pulmonary tuberculosis.

Even with the reduction in the incidence, 50,000 deaths from tuberculosis in the United States occurred in 1947, and the total number of tuberculous patients in this country is about 500,000. According to Birkhaug only half of these persons are under treatment and only one fourth in hospitals and sanatoriums. Almost 180,000 frank cases of tuberculosis are left at large to infect the healthy population. In an attempt to improve a similar situation, Denmark, Norway and Sweden have entered on a nationwide BCG vaccination of the tuberculin-negative population under 50 years of age. In Norway, BCG vaccination was made compulsory in 1947 for all tuberculin-negative persons under 50 years of age.

The rapid decline in tuberculosis mortality has created a new factor of epidemiologic importance; namely, a great number of negative reactors, persons who failed to acquire specific resistance against tubercle bacilli by means of a mild childhood infection. Heimbeck[4] of Norway made the important observation, since verified in other countries, that the victims of tuberculosis among student nurses working in tuberculosis wards were nearly always the tuberculin-negative reactors.

The BCG Advisory Committee of the state of New York[5] reported that BCG vaccination is the only known practical method of reducing morbidity and mortality from tuberculosis. There is a general agreement that it is safe and that it serves to convert nonreactors to tuberculin to reactors through infection with avirulent and benign bovine tubercle bacilli. BCG vaccination has no value in treating tuberculosis.

Madsen of Norway made the important observation that the primary tuberculous complex produced in tuberculin-negative reactors by means of BCG vaccination is sufficient to protect against the progression of a subsequently superimposed virulent infection. The investigations of Heimbeck on student nurses, of Ferguson in Canada[6] and of Rosenthal[7] and his co-workers in Chicago confirmed that vaccination with BCG inhibits primary tuberculosis in a manner analogous with the specific resistance induced by spontaneous and clinically silent infection with virulent tubercle bacilli. The work of Aronson and Palmer[8] among North American Indians is particularly significant because it was carried out on two groups of persons that are as comparable as humanly possible. In terms of cases per thousand person-years, the rates of mortality from tuberculosis were 24.3 and 4.7 respectively.

Birkhaug suggested that BCG vaccine should be recommended for extensive use in the United States in tuberculin-negative reactors in groups occupationally exposed to tuberculous infections and in population groups with high tuberculosis mortality and morbidity, and where there has been a known exposure to tuberculosis or where an exposure is likely to occur.

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OLFACTORY DEPRESSANT

In 1934 Elsberg and Levy[1] suggested a simple method of measuring the acuteness of the sense of smell. The method consisted of injecting different volumes of odorous air into the nasal passages, the smallest volume which produced a sensation of the particular odor being taken as a measure of olfactory acuity. The Elsberg apparatus included bottles of fixed size, each containing a constant amount of odorous substance, such as coffee or citral. The bottles are closed by rubber stoppers, which contain inlet and outlet tubes. A nosepiece ending in two olives is connected with the outlet tube, which is closed with a pinchcock. The inlet tube is connected with a syringe by means of which measured volumes of air can be injected into the bottle. This volume is released into the nasal passages by pressing the pinchcock. The smallest volume of odorous air which produces a sensation of the particular odor three times in succession is recorded, the subject removing the nosepiece and resting for thirty to sixty seconds between tests.

Adopting this technic, Goetzl and Stone[2] of the Permanente Foundation, Oakland, Calif., demonstrated a diurnal cycle in olfactory acuity in human subjects. The pattern of these variations was found to be remarkably constant and intimately connected with the habitual dietary cycle. Meals, if taken at normal intervals, are regularly preceded by a period of increased olfactory acuity and followed by a period of decreased acuity. When food is ingested between meals the precibal increase fails to occur. When a meal is omitted, the postcibal decrease does not develop. The precibal increase in olfactory acuity is apparently a measure of increased appetite, while the postcibal decrease is apparently a measure of the resulting feeling of satiety.

As a practical application of this technic the California physiologists studied the effects on the sense of smell of oral administration of amphetamine sulfate. The ability of this drug to subdue the sensation of hunger is generally accepted. The drug is frequently used as an adjuvant in the treatment of obesity. The physiologic mechanism of this drug's action is still undetermined. Many physicians would attribute its anorexial action to an inhibition of gastric tone,[3] while others would explain it as a result of an elevation of mood with the production of a sense of well-being.[4] The theory that the resulting anorexia is due to a depressant effect on the olfactory sense, however, was suggested by Ivy.[5] This was deduced from his observation that the drug produces anorexia in dogs even after extrinsic denervation of the stomach and intestines.

Goetzl and Stone tested the Ivy theory by measuring the olfactory acuity of persons before and after oral administration of amphetamine sulfate. On the control days when no drug was given the olfactory acuity increased rapidly from 10 a. m. (beginning of experiment) to 12 o'clock. The acuteness then fell precipitately during the lunch period (12 to 1). By the end of this period the sense of smell was depressed below its initial (10 a. m.) level. From 1 p. m. on the acuity gradually increased, reaching about half the prelunch level by 5 p. m. (end of experiment).

On the test days 10 mg. of the drug was given orally at about 10:30 a. m. The normal increase in olfactory acuity did not occur and was replaced by gradual fall in acuity. The olfactory acuity remained subnormal till the end of the test (5 p. m.). There was an acceleration of the dulling effect on the sense of smell as a result of lunch. Similar depressing effects were produced when administration of the drug was delayed till immediately before lunch, and on days when the drug was administered in lieu of lunch. With a freely selected caloric intake at lunch time, there was without exception a 35 to 40 per cent voluntary reduction in caloric intake when the lunch was preceded by administration of the drug. In all subjects the drug produced a sensation of satiety.

From these and other observations Goetzl concludes that the functional state of the olfactory system is important in the regulation of the sensation complex of appetite and satiety and that the anorexia produced by amphetamine sulfate is due primarily to its depressant action on the olfactory sense.

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PSYCHOANALYSIS

Unlike every other medical discipline, the tenets of psychoanalysis question the right or qualification of those who have not themselves been subjected to psychoanalysis to express any valid opinion on the subject.

Recently Hiram K. Johnson,[1] writing in the *Psychiatric Quarterly*, presented a critique of psychoanalysis from a sympathetic yet skeptical and scientifically detached attitude. "In looking over the literature," he says, "one often has the feeling that the Freudian analyst is less concerned with results than with the fact that he is solely in possession of the one system of psychodynamics which purports to be thoroughgoingly scientific. . . . Rather grudgingly it is admitted by analysts that dream interpretation is a somewhat flexible matter and depends to a large extent

1. Johnson, H.: Psychoanalysis—A Critique, Psychiatric Quart. 22:321-338, 1948.

on the preoccupations, values and therapeutic aims which the analyst maintains."

Dr. Johnson points out the close similarity between the problems concerned in psychoanalysis and those dealt with in theology. All of the "neurosis-producing patterns" which freudian analysis attempts to destroy have long been recognized as evil in the eyes of the theologian—long before a scientific terminology was considered. "It will be seen," Johnson states, "that the Freudian psychology regards the adult personality as a composite of Jekylls and Hydes, but is concerned exclusively with the Hydes. These, it sets about to deracinate by the infantile roots, using a bizarre yet historical and sometimes effective method of negative conditioning. The chief weapon, as has been noted, in this bogy hunting is a highly specialized variety of associations which are anything but 'free.'"

Johnson believes that the chief contribution of freudian psychology to the science of human mind may turn out to be that it has stressed the historical development of personality and aided in bringing into focus memories, emotions and attitudes which generally belong to the fringes of consciousness. He says that the history of magic and experimental science reveals a tendency for each successive phase of culture to develop a blind spot for its cults and errors. "Freudian psychoanalysis illustrates this phenomenon [Johnson] and corresponds to the vogue of phrenology and animal magnetism in the preceding century."

Because today so many have a highly emotionally charged attitude toward psychoanalysis and the teaching of the school of Freud, it takes courage to publish such strong statements. If, however, psychoanalysis wishes to claim a place as a scientific subject comparable to that of physiology or pathology, its devotees must be prepared not only to receive such comments but to answer them in a detached and scientific manner which will satisfy the collective intelligence of the scientifically minded.

Current Comment

HYPERTENSION AND PHEOCHROMOCYTOMA

Tumors of chromaffin cells, pheochromocytoma or paraganglioma, are now recognized so frequently they no longer can be regarded as rare. They may occur in true pheochrome tissue anywhere, but they occur most frequently in the adrenal medulla. While usually single, they may be multiple, a fact of special importance in the surgical treatment of such conditions. MacKeith [1] has classed 91 per cent of pheochromocytomas in 165 cases as not cancerous; however, the nature and structure of this type of neoplasma merit more study. The production of epinephrine by the cells of pheochromocytoma is a perfect example of functional activity by neoplastic endocrine cells. As reviewed and studied by Cahill,[2] pheochromocytoma may cause typical hypertension, paroxysmal and also continuous, oftener perhaps in children than in adults. Significant amounts of epinephrine have been demonstrated in the tumor tissue by assay as well as by special staining; abnormal amounts of epinephrine may occur in the blood of the patient. The handling of pheochromocytoma during operation may be dangerous because of release of epinephrine and should be postponed until all vessels surrounding the tumor or connected with it are ligated. If necessary in such circumstances, the immediate fall in pressure can be controlled by intravenous injection of epinephrine. On removal of all the tumor tissue there follows a permanent fall to normal of the blood pressure —a unique cure of hypertension by removal of its cause.

1. MacKeith, R.: Adrenal-Sympathetic Syndrome. Chromaffin Tissue Tumour with Paroxysmal Hypertension, Brit. Heart J. 6:1, (Jan.) 1944.

2. Cahill, G. F.: Pheochromocytomas, J. A. M. A. 138:180 (Sept. 18) 1948.

RHEUMATOID AGGLUTINATING GLOBULIN

A new serum reaction, a possible key to the biochemical puzzle of rheumatoid arthritis, is described by Rose [1] and associates of Columbia University. During complement fixation tests for rickettsialpox, the convalescent serum of a patient was observed to agglutinate unhemolyzed sheep erythrocytes. In addition to having suffered recently from rickettsial infection, the patient was also afflicted with rheumatoid arthritis in an active state. Further investigation revealed that the serum of this patient would agglutinate normal sheep erythrocytes only in dilutions less than 1:16. The same erythrocytes after being sensitized with a small amount of rabbit anti-sheep-amboceptor were agglutinated in a serum dilution as high as 1:2,048, a 128 fold differential titer. A study was then undertaken to determine in what circumstances a similar high differential was present in the serums of other patients. A study of 110 patients showed that a similar high differential occurs almost exclusively in the serums of patients with rheumatoid arthritis and that the agglutinin titer for sensitized sheep cells varies with the activity and severity of the arthritic process. In patients with other arthritic diseases and with clinically inactive rheumatoid arthritis, the differential agglutination titer falls to within normal limits. It is never more than sixteen times the titer of agglutinins for nonsensitized sheep erythrocytes. Differential sheep cell agglutination tests were carried out with the electrophoretically separated globulin in fractions of serums from patients with rheumatoid arthritis. The essential agglutinin occurs apparently quantitatively in the globulin fraction of such serum. The precise nature of this rheumatoid agglutinating globulin, however, has not been determined. These investigators believe that their simple sheep cell differential agglutinin test may be of value in determining the activity status of patients suffering from rheumatoid arthritis. It may also serve as an aid in the differential diagnosis between rheumatoid arthritis and other diseases with arthritic manifestations.

1. Rose, H. M.; Regan, C.; Pearce, E., and Lipman, M. O.: Proc. Soc. Exper. Biol. & Med. 68:1 (May) 1948.

ORGANIZATION SECTION

Official Notes

PROPOSED SCIENTIFIC PROGRAM AT INTERIM SESSION

Nov. 30-Dec. 3, 1948

Auditorium, St. Louis

TUESDAY, NOVEMBER 30

P. M.

2:00 Lecture in Opera House on Hypertension. Irvine H. Page, Cleveland.

2:30 Lecture in Opera House on Problems of Delivery. Ralph Reis, Chicago.

3:00 Intermission.

3:30-5:00 Clinical Presentations on Obstetrics in Room 8-1; Poliomyelitis in Room 8-2; Arthritis in Room 8-3; Cancer in Room 8-6; Radiology in Room 8-7; Laboratory in Room 8-8, and Hypertension in Room 8-10.

WEDNESDAY, DECEMBER 1

A. M.

9:00 Lecture in Opera House on Pediatrics. (Speaker to be announced.)

9:30 Lecture in Opera House on Position of the Laboratory in the Diagnosis and Control of Disease. F. W. Konzelmann, Atlantic City, N. J.

10:00 Intermission.

10:30-12:00 Clinical Presentations on Pediatrics in Room 8-1; Poliomyelitis in Room 8-2; *Diabetes in Room 8-3; Dermatology in Room 8-6; Radiology in Room 8-7; Laboratory in Room 8-8, and Hematuria in Room 8-10.

P. M.

2:00 Lecture in Assembly Room 1 on Arthritis. (Speaker to be announced.)

2:30 Lecture in Assembly Room 1 on Common Skin Diseases. Everett Fox, Dallas, Texas.

3:00 Intermission.

3:30-5:00 Clinical Presentations on Obstetrics in Room 8-1; Poliomyelitis in Room 8-2; Diabetes in Room 8-3; Cancer in Room 8-6; Radiology in Room 8-7; Laboratory in Room 8-8, and Heart in Room 8-10.

THURSDAY, DECEMBER 2

A. M.

9:00 Lecture in Opera House on Hematuria. (Speaker to be announced.)

9:30 Lecture in Opera House on Jaundice. Sidney Portis, Chicago.

10:00 Intermission.

10:30-12:00 Clinical Presentations on Pediatrics in Room 8-1; Poliomyelitis in Room 8-2; *Diabetes in Room 8-3; Dermatology in Room 8-6; Jaundice in Room 8-7; Laboratory in Room 8-8, and Hematuria in Room 8-10.

10:00 a. m. to 1:00 p. m.*

P. M.

2:00 Lecture in Opera House on Diagnosis and Early Treatment of Poliomyelitis. Thomas Gucker, Boston.

2:30 Lecture in Opera House on Heart. George B. Herrmann, Galveston, Texas.

3:00 Intermission.

3:30-5:00 Clinical Presentations on Obstetrics in Room 8-1; Poliomyelitis in Room 8-2; Diabetes in Room 8-3; Cancer in Room 8-6; Jaundice in Room 8-7; Laboratory in Room 8-8, and Heart in Room 8-10.

FRIDAY, DECEMBER 3

A. M.

9:00 Lecture in Opera House on Cancer. C. P. Rhoads, New York.

9:30 Lecture in Opera House on Diabetes. E. P. Joslin, Boston.

10:00 Intermission.

10:30-12:00 Clinical Presentations on Pediatrics in Room 8-1; Poliomyelitis in Room 8-2; Arthritis in Room 8-3; Dermatology in Room 8-6; Jaundice in Room 8-7; Laboratory in Room 8-8, and Hematuria in Room 8-10.

Washington Letter

(From a Special Correspondent)

Oct. 14, 1948.

Cost in Mental Hospitals Up 65 Per Cent

Statistics compiled by Mental Hygiene Division, U. S. Public Health Service, demonstrate the increasing cost of maintaining mental hospitals. Expenditures by such institutions, public and private, totaled approximately $400,000,000 in 1947, an increase of $154,000,000 over the figure for 1945, according to Public Health Service estimates. On a per capita basis, the increase was from $470 per patient in 1945 to $731 last year. It was pointed out by the Mental Hygiene Division that the steep rise is reflective not only of higher general price levels but also of improvement in quality of care given in mental hospitals during the early postwar years. Average daily resident patient population during 1947 was 540,000, compared with 525,000 in 1946 and 513,000 in 1945.

Illness and Off-Job Accidents Cause Most Absenteeism

Three fifths of the absenteeism among manufacturing workers results from illness and accidents away from work, according to findings of a joint study conducted by the Bureau of Labor Statistics, the Social Security Administration and the U. S. Public Health Service. The survey covered two hundred and forty-six plants in 1947. The average employee lost 9.6 working days during the year, of which illness and nonindustrial accidents accounted for 6.5 days, personal reasons 2.5 days and industrial injuries only 0.6 day. Seasonally, absenteeism rates were highest in the year's first quarter (when respiratory infections are at their height), declined substantially in the second, reached the lowest point in the third quarter and rose sharply in the fourth quarter.

Seven Military Medical Research Bases Inspected

The medical sciences committee of the Research and Development Board recently completed its first field trip, in the course of which it visited Army, Navy and Air Force research units at the following locations: Aero Medical Laboratory, Philadelphia; Special Devices Center, Sands Point, Long Island; Army-Navy Medical Procurement Office, Fort Totten, N. Y.; Climatic Laboratory, Lawrence, Mass.; U. S. Submarine Base, New London, Conn.; Army Nutritional Laboratory, Chicago; Aero Medical Laboratory, Wright-Patterson Air Force Base, Dayton, Ohio.

BCG Vaccinations in Alaska Progressing

The Bureau of Indian Affairs (Interior Department) has announced completion of its BCG vaccination program at Point Barrow, Alaska. Dr. Joseph D. Aronson, of Philadelphia, examined 600 Eskimos at the remote Alaskan outpost, and 250 of them received the antituberculosis vaccine. Similar work was done subsequently at Sitka and Wrangell, where 74 persons were vaccinated. Assisting Dr. Aronson were Drs. William Carr, contract physician in the service of the Navy Department; Elaine Schwinge, of the Territorial Department of Health; Ed Gloomquist, of Public Health Service, and Florence Marquis, detailed by the Public Health Service to the Territory of Alaska.

Advisory Committee to Children's Bureau Formed

The recently formed advisory committee to the Children's Bureau (Federal Security Agency) on federal-state programs for maternal and child health and services to crippled children held its first meeting in mid-September, and Dr. Harry H. Gordon, professor of pediatrics at University of Colorado Medical Center, was elected chairman. Serving with him are the following: Drs. Raymond B. Allen, Allan M. Butler, W. W. Bauer, Dean A. Clark, William J. Darby, M. Edward Davis, Kenneth A. Easlick, Nicholson J. Eastman, William T.

Green, Charles F. Good, Harry H. Gordon, John P. Hubbard, Herbert R. Kobes, William Mengert, James Raglan Miller, Oscar L. Miller, Harry A. Ong, John Z. Preston, Abraham Barhash, Duncan E. Reid, Hugh B. Robins, Nathan Sinai, Thomas E. Shaffer, Ernest Stebbins, Felix J. Underwood, Abram L. Van Horn, R. M. Walls and James L. Wilson; also, George Bugbee, executive director, American Hospital Association; Harriett M. Bartlett, Simmons College; Hazel Corbin, R.N., New York Maternity Center Association; Claudia Durham, R.N., Meharry Medical College; Mrs. Lulu Evanson, National Farmers Union; Katharine Faville, R.N., dean, Wayne University College of Nursing; Lawrence J. Linck, executive director, National Society for Crippled Children and Adults; Mary Blanche Moss, executive secretary, American Association of Medical Social Workers; Ewell Newman, National Urban League; Harry Read, Congress of Industrial Organizations; Raymond Rich, New York City; Edward S. Rogers, University of California School of Public Health; Catherine E. Sheckler, R.N., American Nurses' Association; Randel Shake, American Legion; Florence C. Thorne, American Federation of Labor; Mrs. Roy C. F. Weagley, American Farm Bureau Federation; Barbara White, American Physiotherapy Association; Mrs. Eva Ylvisaker, American Dietetic Association; Mrs. C. D. Lowe, National Congress of Parents and Teachers; Mrs. Stella Scurlock, General Federation of Women's Clubs, and Mrs. Edith Hyslop Sherrard, American Association of University Women.

Meetings of the committee will be twice yearly, or oftener, at the call of the Children's Bureau.

Organize Advisory Body on Streptococcus Infections

Newest branch of the Army Epidemiological Board to be formed is the Commission on Streptococcal Infections, which held its organization meeting in Washington September 20. The chairman is Dr. W. S. Tillett, of New York City. From three to five members and about six associate members will comprise the commission, whose composition is not yet completed. The September 20 meeting was devoted largely to discussion of major problems which will confront the unit, including the need of stimulating research in order to gather more information on World War II incidence in the armed forces, basic immune processes and the various types of streptococci. Also discussed were plans for studies on prophylaxis, utilizing penicillin and sulfonamide compounds, which the Army will conduct this winter at certain camps in the Rocky Mountain area of the country.

The Army Epidemiological Board's Commission on Virus and Rickettsial Diseases, of which Dr. John R. Paul is director, will meet on September 30 to discuss the recent outbreak of Japanese B encephalitis in Japan, which to date has claimed an estimated 6,000 cases.

Commission Announces Fellowship Awards

Award of one hundred and sixty-two research fellowships in the biologic, physical and agricultural sciences has been announced by the Atomic Energy Commission. The successful applicants, representing thirty states, will study in forty-three research and educational institutions. Three of the five postdoctoral biologic fellowships awarded will be taken at the University of California and one each at New England Deaconess Hospital (Boston) and Harvard University. All but nineteen of the awards are predoctoral fellowships, whose fields of study will include biologic action of radiation, tracer studies, pathologic effects of radioactive iodine, mechanism of vitamin D activity, hormone investigations and health physics.

Supplies Marked for October Sales

Hospital and laboratory equipment, drugs and miscellaneous supplies are included among federal war surplus property which will be placed on sale by the War Assets Administration in October. Information on the sales, which will be conducted in various parts of the country, may be obtained from the War Assets Administration offices in Chicago, Detroit, Cincinnati, St. Louis, Philadelphia, and Trenton and Linden, N. J.

Booklet Describes Dangers of Abandoned Mines

A booklet, "Hazards of Entering Old Workings," recently issued by Bureau of Mines (Department of Interior) describes the perils to health and limb that lurk in abandoned mines, quarries and open pits. Anoxia and gas poisoning, illness caused by drinking polluted water, snakebites and spider stings, cave-ins—these are among the hazards cited. "Hazards of Entering Old Workings," also known as Information Circular 7479, may be obtained without cost from the Bureau of Mines, Publications Distribution Section, 4800 Forbes Street, Pittsburgh 13, Pa.

Coming Medical Meetings

American Medical Association Interim Session, St. Louis, Municipal Auditorium, Nov. 30-Dec. 3. Dr. George F. Lull, 535 N. Dearborn St., Chicago 10, Secretary.

Annual Conference of State Secretaries and Editors, St. Louis, Hotel Statler, Nov. 28-29. Dr. George F. Lull, 535 N. Dearborn St., Chicago 10, Secretary.

National Medical Public Relations Conference, St. Louis, Hotel Statler, Nov. 27. Mr. Lawrence W. Rember, 535 N. Dearborn St., Chicago 10, Director.

American Academy of Dermatology and Syphilology, Chicago, Palmer House, Dec. 5-9. Dr. Earl D. Osborne, 471 Delaware Ave., Buffalo, Secretary.

American Academy of Ophthalmology and Otolaryngology, Chicago, Palmer House, Oct. 10-15. Dr. W. L. Benedict, 100 First Avenue Bldg., Rochester, Minn., Secretary.

American Academy of Pediatrics, Atlantic City, Chalfonte-Haddon Hall, Nov. 20-23. Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill., Secretary.

American Association of Railway Surgeons, Chicago, Nov. 21-23. Dr. Raymond B. Kepner, 547 W. Jackson Blvd., Chicago 6, Secretary.

American Clinical and Climatological Association, Hot Springs, Va., The Homestead, Nov. 8-10. Dr. James Bordley III, Bassett Hospital, Cooperstown, N. Y., Secretary.

American College of Surgeons, Los Angeles, Biltmore Hotel, Oct. 18-22. Dr. Paul B. Magnuson, 40 E. Erie St., Chicago 11, Secretary.

American Public Health Association, Boston, Nov. 8-12. Dr. Reginald M. Atwater, 1790 Broadway, New York 19, Executive Secretary.

American Society for the Study of Arteriosclerosis, Chicago, Hotel Knickerbocker, Oct. 31-Nov. 1. Dr. O. J. Pollak, Quincy City Hospital, Quincy 69, Mass., Secretary.

American Society of Anesthesiologists, St. Louis, Hotel Statler, Nov. 4-6. Mr. John H. Hunt, 188 W. Randolph St., Chicago 1, Executive Secretary.

American Society of Clinical Pathologists, Chicago, Oct. 10-16. Dr. A. S. Giordano, 531 N. Main St., South Bend 1, Ind., Secretary.

Association for Research in Nervous and Mental Diseases, New York, Waldorf-Astoria Hotel, Dec. 10-11. Dr. Clarence C. Haro, 700 W. 168th St., New York 32, Secretary.

Association of Military Surgeons of the United States, San Antonio, Texas, Nov. 11-13. Dr. James M. Phalen, Army Institute of Pathology, Washington 25, D. C., Secretary.

Indiana State Medical Association, Indianapolis, Oct. 26-28. Mr. Ray E. Smith, 23 E. Ohio St., Indianapolis 4, Executive Secretary.

International College of Surgeons, U. S. Chapter, St. Louis, Kiel Auditorium, Nov. 16-19. Mr. Ralph E. Osborne, 1516 Lake Shore Drive, Chicago, Business Secretary.

Inter-State Postgraduate Medical Association of North America, International Medical Assembly, Cleveland, Public Auditorium, Nov. 9-12. Dr. Tom B. Throckmorton, 406 Sixth Ave., Des Moines, Iowa, Secretary.

Oklahoma City Clinical Society, Oklahoma City, Biltmore Hotel, Oct. 25-28. Mrs. M. R. Waller, 512 Medical Arts Bldg., Oklahoma City, Executive Secretary.

Omaha Mid-West Clinical Society, Omaha, Hotel Paxton, Oct. 25-29. Dr. John M. Thomas, 1031 Medical Arts Bldg., Omaha 2, Secretary.

Puerto Rico, Medical Association of, Santurce, Dec. 10-12. Dr. J. Basora Defillo, Box 3866, Santurce, Secretary.

Radiological Society of North America, San Francisco, Dec. 5-10. Dr. Donald S. Childs, 607 Medical Arts Bldg., Syracuse 2, New York, Secretary.

Southern Surgical Association, White Sulphur Springs, W. Va., Dec. 7-9. Dr. Alfred Blalock, Johns Hopkins Hospital, Baltimore 5, Secretary.

Southwestern Medical Association, El Paso, Texas, Oct. 28-30. Dr. Wickliffe R. Curtis, First National Bank Bldg., El Paso, Secretary.

Western Surgical Association, St. Louis, Dec. 2-4. Dr. Warren H. Cole, 1853 W. Polk St., Chicago 12, Secretary.

Virginia, Medical Society of, Richmond, John Marshall Hotel, Oct. 18-20. Miss Agnes V. Edwards, 1200 E. Clay St., Richmond 19, Secretary.

GOVERNMENT SERVICES

PUBLIC HEALTH SERVICE

COST OF LONG TERM MENTAL CARE

During 1947 the cost of providing long term hospital care in mental hospitals was approximately $400,000,000, according to estimates of the Mental Hygiene Division of the Public Health Service. Between 1945 and 1947, expenditures for maintenance in hospitals providing long term care for psychiatric patients increased by $146,000,000, or approximately 60 per cent of the estimated expenditures for 1945. In terms of the annual cost per patient, or per capita expenditure, the increase was about 50 per cent, from $480 in 1945 to $727 in 1947. This increase reflects in large part the increase in the general price level during the period but may also reflect to some degree improvement in the quality of mental hospital care during the postwar period.

The estimates presented here are based on figures from a variety of sources. For state, psychopathic and Veterans Administration neuropsychiatric hospitals these figures are reasonably complete; for county and city hospitals and private hospitals, however, the basic data are somewhat fragmentary; the estimates are in some instances based on the assumption of a constant relationship between annual changes for these two types of hospitals, respectively, and corresponding changes for state hospitals. In view of this situation, estimates of expenditures have been rounded to the nearest million, and those of average daily population to the nearest thousand. Figures on per capita expenditures are based on the initial unrounded absolute numbers.

ADVANCED TRAINING FOR MEDICAL OFFICERS

Six officers of the U. S. Public Health Service have been awarded Rockefeller fellowships for graduate study in public health. They are Surgeons Elton Osborne Jr. and Mary Walton, and Assistant Surgeon Clarence A. Velat, at Johns Hopkins University; Senior Surgeon (R) S. J. Axelrod, at the University of Michigan; Senior Assistant Surgeon George Adams, at Yale, and Senior Assistant Surgeon George A. Spendlove, at Harvard.

Other Public Health Service officers receiving advanced training are Surgeons Samuel C. Ingraham, who is beginning a year's training in radiobiology at the University of Colorado Medical School, Denver; John B. Vander, at the Massachusetts Institute of Technology for part time training in radiobiology; and Senior Surgeon Kirkland C. Brace, at University of Chicago for advanced training in radiobiology. Surgeon Mary A. Diamond is assigned to the Columbia University College of Physicians and Surgeons, New York, for study in neurology and psychiatry; Senior Surgeon Vernam T. Davis is in psychiatric training at William A. White Institute of Psychiatry, New York; Senior Assistant Surgeon Robert B. Dorsen will attend the University of Pennsylvania for a year's study in obstetrics and gynecology; Senior Assistant Surgeon Rheim M. Jones will attend the New York Postgraduate Medical School for a course in surgery of the eye, and Senior Assistant Robert C. Rodger will study pathology and diagnostic bacteriology at Johns Hopkins University.

FEDERAL GRANTS FOR UNDERGRADUATE COURSES

The U. S. Public Health Service announces that federal grants for undergraduate courses are now being offered to medical schools to foster training of students in the mental aspects of disease. Formerly, grants to medical schools authorized by the National Mental Health Act were used primarily for graduate training in psychiatry. The extension of these grants to the undergraduate field was recommended by the National Advisory Mental Health Council as a means of providing future physicians with the basic knowledge that will help them recognize early symptoms of mental illness, treat cases which do not require the service of a specialist and apply psychiatric treatment to various types of illness.

Applications should be made to the Mental Hygiene Division of the Public Health Service, Washington, D. C., by Oct. 15, 1948. Some selection of schools will be necessary, because of limited funds, although eventually it is expected that all medical schools that desire such assistance may receive grants. The amounts to be allocated to each school selected will be based on the recommendation by the National Mental Health Council, but with the funds now available it will not be possible to grant more than $37,500 to a school for the first three year period.

DIAGNOSTIC CANCER TESTS

The National Cancer Institute and a group of medical schools and hospitals will cooperate in a program to determine which of the many reported diagnostic tests are dependable, and in refining the most promising tests and in developing new tests. The Director of the National Cancer Institute, Dr. J. R. Heller, states that negotiations leading up to this program have been in progress the past year and have resulted in a tentative program which includes clinical and laboratory studies carried out simultaneously in the cooperating medical schools and hospitals with the necessary coordination and direction centering in the National Cancer Institute. Tests that show promise in the laboratories will first be applied to a small number of thoroughly studied cases and then, if justified, to thousands of persons with and without cancer, particularly to those passing through the United States Public Health Service Medical Center at Hot Springs, Ark., where National Cancer Institute already operates a pilot cancer detection unit.

MISCELLANEOUS

THE GOVERNMENT NEEDS PHYSICIANS

The United States Civil Service Commission announces an examination for filling medical officer positions open in some twenty-eight medical fields ranging from general practice through the various specialties. The positions are located in Washington, D. C., throughout the United States and in the Panama Canal Zone, in such agencies as the Indian Service, Panama Canal Service, United States Public Health Service, Department of the Army, Veterans Administration, Civil Aeronautics Administration, and the Railroad Retirement Board. The salaries range from $4,479 to $6,235 a year.

No written test will be required. To qualify, applicants must be graduates of a medical school and must be currently licensed to practice medicine and surgery. For positions paying $4,479 and $5,232, applicants must have completed a full internship, either general rotating or in a specialty (this requirement is waived for some positions); and for positions paying $5,232 and $6,235, they must have had professional medical experience. Maximum age limits are as follows: for Panama Canal Service, 45 years; for Indian Service, 50 years; for other agencies, 62 years. For persons entitled to veteran preference, the 45 and 50 year age limits are waived to 62 years, and the 62 year age limit is waived without limitation.

Information and application forms may be secured at most first and second class post offices, from Civil Service regional offices, or from the United States Civil Service Commission, Washington 25, D. C. Applications will be accepted in the Commission's Washington office until further notice.

Medical News

(Physicians will confer a favor by sending for this department items of news of general interest: such as relate to society activities, new hospitals, education and public health. Programs should be received at least two weeks before the date of meeting.)

CALIFORNIA

Nutrition Study of Aged.—A nutrition study of older people is being conducted in San Mateo County through the cooperation of the local health department, the College of Agriculture for the University of California at Berkeley, the U. S. Department of Agriculture, the U. S. Public Health Service and the California Department of Public Health. Federal agencies are supplying a team of experts who will be guided by an advisory committee representing various California health and agricultural agencies. The study will attempt to determine the nutritional status of a selected group of institutionalized and noninstitutionalized aged persons.

COLORADO

Professor Schmidt Goes to New Orleans.—Dr. Ernest A. Schmidt has resigned as professor and head of the department of radiology of the University of Colorado Medical Center to take up new duties at Touro Infirmary, New Orleans. The department of radiology will be under the administration of a departmental committee until a new professor and head of the department can be appointed.

Research on Epilepsy.—The University of Colorado Medical School, Denver, has received a grant of $5,000 from the Easter Seal fund of the Colorado Division of the National Society for Crippled Children and Adults for treatment and research in the field of epilepsy. The university's program will be headed by Dr. Harriot H. Hunter of the Epilepsy Clinic. The grant provides for a director, honorariums for two medical assistants and a social worker and for administrative services and supplies. The program calls for a registry of epileptics and a work shop to provide group therapy for parents as well as patients.

DISTRICT OF COLUMBIA

Appoint Professor of Urology.—Dr. Lloyd G. Lewis, associate professor of urology, has been appointed professor of urology at the Georgetown University Medical Center. A graduate of Johns Hopkins University School of Medicine, Baltimore, 1928, Dr. Lewis served as an instructor, associate, and assistant professor of urology there and assistant visiting urologist at Johns Hopkins University Hospital, 1933-1942. He served in the army during World War II as chief of the urologic section of the Walter Reed General Hospital. He is now a consultant in genitourinary surgery to the Secretary of War and Walter Reed General Hospital.

DELAWARE

Dedicate the Governor Bacon Health Center.—This center, which is a part of the Delaware State Hospital at Farnhurst, was dedicated September 27. It will accommodate 282 children in various psychotic states, epileptics without psychoses, crippled children or children waiting for assignment to foster homes, and 266 adults, who are epileptic, alcoholic or senile and bedridden. The center will provide modern diagnostic and therapeutic facilities. Its objective is complete or partial rehabilitation of children on the statewide basis for all classes of people. It will also be an educational and training center and will closely affiliate with the New York and Pennsylvania universities, the Alfred I. DuPont Institute, Delaware State Hospital and all general hospitals and the health and welfare agencies of the state.

ILLINOIS

Two Day Institutes on Venereal Disease.—The Illinois Department of Health, through its divisions of venereal disease control and public health nursing, is sponsoring three two-day institutes on venereal disease control. The first is scheduled for November 15-16 at the Kaskaskia Hotel in LaSalle, the second on November 17-19 at the St. Nicholas Hotel in Springfield and the third on November 23-24 at the Hotel Emmerson in Mt. Vernon. Some of the subjects to be discussed are: Facilities for the Treatment of Venereal Diseases, Health Education and Venereal Diseases Control, and Drugs Used in the Treatment of Gonorrhea.

Evanston Hospital Expands.—Three additions are planned for the Evanston Hospital. Ground-breaking ceremonies October 1 marked the beginning of a six story addition to the west end of the main building and a two story connection with the Abbott Memorial Laboratory. The new building will add ninety-two beds. The second building in the expansion program will be a maternity building, and the third will provide facilities for psychiatric care and tuberculous patients, a pediatrics division, a dental clinic and a tumor clinic in connection with the outpatient department.

Chicago

Dr. Harvey to Address Institute of Medicine.—Dr. A. McGehee Harvey, professor of medicine, Johns Hopkins University School of Medicine, Baltimore, will deliver the annual lecture before the Institute of Medicine of Chicago and the Chicago Society of Internal Medicine October 22 at the Palmer House on "Some Physiological Experiments of Nature in the Field of Neuromuscular Function. Potassium Deficiency, Potassium Intoxication, Myasthenia Gravis."

Prize for Paper on Surgery.—The Chicago Surgical Society awards an annual prize for a manuscript describing experimental work in one or both fields of experimental and clinical surgery. Applicants must be residents of Cook County. All identification marks of the author and of the hospital or institution in which the work was performed must be eliminated from the manuscript. The paper should be submitted to the Secretary, Dr. C. B. Pruestow, Room 910, 30 N. Michigan Avenue, not later than March 1, 1949, accompanied by a sealed envelope bearing on its outside the title of the paper and containing within it the name and address of the author.

Medal Awarded to a Dog.—The National Society for Medical Research on October 1 presented a medal to an experimental animal, a dog, for its part in the advancement of research on cardiovascular surgery. The presentation was made by Dr. Andrew C. Ivy, vice president of the University of Illinois, on a televised program over station WBKB. Seventy-six children in the Chicago area owe their lives to this dog, Caesar, which played a part in the original research at Children's Memorial Hospital. Two former "blue babies" also appeared on the program. The presentation was part of a health education program of the American Medical Association developed in cooperation with the educational committee of the Illinois State Medical Society and the National Society for Medical Research.

Eight Professors Appointed.—Appointment of eight physicians to positions of professorial rank on the faculty of the University of Illinois College of Medicine have been announced: Dr. S. Howard Armstrong Jr., has been appointed professor of medicine. A graduate of Princeton University, Princeton, N. J., and Harvard Medical School, Boston, 1937, Dr. Armstrong now serves as chairman of the department of medicine at Presbyterian Hospital. Drs. William S. Hoffman and Robert Eugene Johnson have been named professorial lecturers in physiology. Dr. Hoffman serves as director of biochemistry at Cook County Hospital Laboratories and Hektoen Institute for Medical Research. Dr. Johnson holds the position of director of research at the Army Medical Nutrition Laboratory. Drs. Samuel A. Leader and Harry Slobodin have been appointed to the faculty with the rank of clinical assistant professor of radiology. Dr. Leader, a graduate of the University of Chicago and Rush Medical College, is chief of diagnostic x-ray at Vaughn Unit, Veterans Administration Facility, Hines. Dr. Slobodin, a graduate of Columbia University and New York University College of Medicine, New York, has served as chief of the department of radiology at the Veterans Hospital since 1942. Dr. Rudolph G. Novick, director of the Illinois Society for Mental Hygiene, has been appointed clinical assistant professor of psychiatry. Joseph E. Bourque, Ph.D., has been appointed an assistant professor of physiology. He previously taught at Wayne University College of Medicine, Detroit. Dr. James A. Campbell has received an appointment as assistant professor of medicine. A graduate of Knox College, Galesburg, Ill., and Harvard Medical School, Boston, he now serves as assistant attending physician at Presbyterian Hospital.

IOWA

Otolaryngology Conference.—The State University of Iowa College of Medicine, Iowa City, is sponsoring a conference in otolaryngology November 29-December 3. Guest speakers will be Drs. Kenneth M. Day, Pittsburgh; French K. Hansel, St. Louis; Frederick T. Hill, Waterville, Maine; Paul H. Holinger, Chicago; Gordon D. Hoople, Syracuse, N. Y.; Julius Lempert, New York, and James H. Maxwell, Ann Arbor, Mich. Enrollment is limited to 25, and the registration fee is $75. Inquiries and applications should be addressed to Dr. J. T. McClintock, Director of Postgraduate Studies, Room 259, Medical Laboratory Bldg., Iowa City.

V 1
194

Public Health Appointment.—Dr. Ralph H. Heeren, formerly of the Oklahoma City Health Department, has taken over duties as director of Preventable Diseases and Venereal Disease for the Iowa State Health Department. He succeeds Dr. Carl F. Jordan, resigned. Dr. Heeren obtained his medical degree from the State University of Iowa College of Medicine, Iowa City, 1934, and did graduate work at Western Reserve University, Cleveland, and at Harvard School of Public Health, Boston. He has taught medical bacteriology at the State University of Iowa, Western Reserve and Tulane University of Louisiana School of Medicine, New Orleans. He has had experience in state health work in Iowa, Louisiana and Oklahoma.

MICHIGAN

Record Attendance.—Registration records were broken at the annual meeting of the Michigan State Medical Society in Detroit, September 22-24. A total of 3,382 attended the three day postgraduate conference, 2,734 of which were doctors of medicine.

Dr. Stevenson Appointed Professor of Obstetrics.—Dr. Charles S. Stevenson, formerly of Boston, has been appointed professor of obstetrics and gynecology and head of the department at Wayne University College of Medicine, Detroit. Dr. Stevenson received his medical degree at Johns Hopkins School of Medicine, Baltimore, and was resident gynecologist at the hospital and resident obstetrician at the Boston Lying-In Hospital.

Sight-Saving Program.—The Michigan State Department of Health reports that poor eyesight handicaps 1 out of every 5 Michigan school children. Last year the department undertook a vision conservation program to help local agencies and groups in the prevention and correction of sight defects of children and improving the visual environment in school and in homes. The department's vision consultant was invited into 27 counties and to teacher's colleges, institutes and workshops. Nine counties carried on a program in which the sight of all school children was tested. Of 31,585 children tested, 3,864 showed some sight defects. In addition, there were 2,748 children who were under treatment or who had undergone treatment for eye conditions. Equipment, material and the services of the vision consultant are available on request through the local health department or, where there is no such department, directly through the Michigan Department of Health, Lansing 4, Mich.

MINNESOTA

Lecture on Gastric Secretion.—The second annual Phi Delta Epsilon medical lectureship will be given at the University of Minnesota, medical sciences amphitheater, November 3, 8 p. m., by Franklin Hollander, Ph.D., head of the Gastroenterology Research Laboratory of the Mount Sinai Hospital, New York, on "Studies in Gastric Secretion." The lecture is presented under the combined auspices of the University of Minnesota Medical School, the Phi Delta Epsilon undergraduate fraternity and the Minnesota Phi Delta Epsilon graduate club.

NEW YORK

Open New Psychiatric Wing.—Strong Memorial Hospital's new $1,000,000 psychiatric wing at Rochester was opened for study and treatment of the emotionally ill August 27. Present services for a time will be restricted to outpatient visits daily.

Postgraduate Courses.—The Medical Society of the State of New York, in cooperation with the New York State Health Department, has arranged a postgraduate lecture at the University Club, Syracuse, October 19, at 8:30 p. m. Dr. Isadore Snapper, New York, will speak on "Osseous Manifestations of Medical Diseases." A series of postgraduate lectures have been arranged for the Shoharie County Medical Society on Tuesday afternoon at 4 o'clock at the Cobleskill High School Building, Cobleskill.

Oct. 19—Chester E. Clark, Syracuse, Gynecology in General Practice.
Nov. 2—Richard S. Farr, Syracuse, Disabilities of the Foot and Ankle.
Nov. 16—Ethel G. Cermak, Albany, Rheumatic Fever.
Nov. 30—Alfred Weintraub, New York, The Ophthalmoscope in the Diagnosis of General Diseases.

On November 17 the Sullivan County Medical Society will hear Dr. Paul A. Bunn, Syracuse, speak on "Recent Advances in Therapy" at the Monticello Hospital, Monticello, 8:30 p. m.

The Onondaga County Medical Society will hear Dr. Alexander Brunschwig, New York, speak on "Radical Surgery for Cancer" at a meeting at the University Club, Syracuse, November 9, 8:30 p. m.

Advisory Council to Aid in State Mental Health Program.—An advisory council, representing various aspects of community activity in the fields of psychiatry, social welfare, general medicine and public health, has been appointed to advise the Department of Mental Hygiene in the expansion of New York State's mental health program. It will meet monthly with the commissioner of mental hygiene, Dr. Frederick MacCurdy. Dr. Howard W. Potter, professor of psychiatry at the Long Island College of Medicine, is chairman of the council. Other members are: Dr. Edward A. Sharp, New York; Dr. S. Bernard Wortis, New York, representing the Medical Society of the State of New York; Dr. J. Lawrence Pool, New York; Dr. L. Whittington Gorham, Albany; Marian F. McBee, executive secretary of the New York Committee on Mental Hygiene; Ralph King, president of the New York State County Welfare Association, and Henry J. A. Collins, judge of the Children's Court in Nassau County. Among the projects on which the council will aid the commissioner and his staff is a more comprehensive educational program to promote mental health of children. The council will also assist the department in securing cooperation with hospitals and developing plans for improving care of mentally ill patients in general hospitals.

New York City

Personal.—Dr. I. Paul Train was recently promoted to assistant professor of surgery at New York Medical College and assistant attending surgeon at Flower-Fifth Avenue Hospital. He is a graduate of New York Medical College, Flower and Fifth Avenue Hospitals, 1930.

First Harvey Lecture.—Dr. Cecil J. Watson, professor of medicine, University of Minnesota Medical School, will deliver the first Harvey Lecture on "Urobilin and Stercobilin" before the members of the Harvey Society in affiliation with the New York Academy of Medicine October 26, at 8:30 p. m.

Wilson Memorial Lecture.—Dr. Anton J. Carlson, professor emeritus of physiology, University of Chicago, will lecture on "Diet and the Span of Life," October 19 at 4:15 p. m., in the North Lounge of Hunter College. This is the second in the annual Margaret Barclay Wilson Memorial Lecture series, established by the department of physiology, health and hygiene, Hunter College, as a tribute to the memory of its first chairman.

Symposium on Rehabilitation.—The Association of Military Surgeons of the United States, Metropolitan New York Chapter, will hold a Symposium on Rehabilitation at the New York University Bellevue Institute of Rehabilitation and Physical Medicine, October 27 at 8:30 p. m. The speakers will be:

Howard A. Rusk, The Place of Rehabilitation in the Practice of Medicine.
Donald A. Covalt, Rehabilitation—Its Place in the General Hospital.
Morris Grayson, Emotional Factors in Physical Disability.
George G. Deaver, Rehabilitation of Motor Disabilities.

Sixteenth Series of Salmon Lectures.—Torbjoern O. Caspersson of the Nobel Institute, Stockholm, will give the sixteenth series of the Thomas William Salmon Lectures at the New York Academy of Medicine on the evenings of November 8-10, under the general title of "Cell Function and Cell Growth in Normal and Pathologic Conditions, Studied by Quantitative Cytochemical Procedures." Dr. Caspersson, biophysicist and biochemist, is professor of medical cell research and genetics and director of the Institute for Cell Research of the Medical Nobel Institute in Stockholm.

OHIO

Tuberculosis Clinics.—The Westside County Tuberculosis Clinic opened September 21 as an outpatient department of Sunny Acres Sanatorium, Cleveland, in cooperation with the Sixth Health District. Open daily, it will operate as a diagnostic and case-finding clinic. Another clinic is now under construction on the east side of the city and will be finished within a year. These new clinics together with the new Cleveland Health Center to be opened by the end of 1948, the other health centers now operating and the three county mobile x-ray units will provide Cleveland with excellent facilities for tuberculosis case finding.

Course in Chest Diseases.—The Ohio State Medical Association is offering a postgraduate course in Diagnosis and Treatment of Chest Diseases at the Elks Home, Chillicothe, October 21, beginning at 2 p. m. Physicians from all sections of the state are invited. Speakers will be:

John H. Skavlem, Cincinnati, Pathogenesis and Clinical Considerations.
William L. Potts, Columbus, Laboratory Aids in Diagnosis of Pulmonary Diseases.
David W. Heusinkveld, Cincinnati, Chest Films.
Joseph B. Stocklen, Cleveland, Planning the Management of the Tuberculous Patient.
Maurice G. Buckles, Columbus, Developments in Chest Surgery.
Sidney E. Wolpaw, Cleveland, Drug Therapy.
Arnold R. Kurlander, Columbus, Community Tuberculosis Control Measures.
John H. Skavlem, Cincinnati, Panel Discussion.

OREGON

State Medical Election.—At the meeting of the Oregon Medical Society, September 15-18, Dr. Leslie S. Kent, Eugene, was installed as president and Dr. James E. Buckley, Portland, was named president-elect; Dr. Werner E. Zeller, Portland, secretary, and Dr. Allen O. Pitman, Hillsboro, treasurer.

Appointed to Board of Health.—The Oregon State Board of Health has appointed Dr. George C. Gibson, Ravenna, Ohio, as director of the cancer section of the state department of health. Dr. Gibson received his medical degree from Harvard Medical School, Boston, in 1943, served with the U. S. Public Health Service Marine Hospital, Brighton, Mass., and for two years at the Ponderville Hospital at Walpole.

PENNSYLVANIA

To Direct State Bureau of Laboratories.—Arthur P. Hitchens, Lieutenant Colonel (M.C.), U. S. A., retired, formerly professor of public health and preventive medicine at the University of Pennsylvania School of Medicine, Philadelphia, has been appointed to succeed Dr. Claude P. Brown as director of the Bureau of Laboratories of the Pennsylvania State Department of Health. Dr. Brown has been connected with the bureau for seven years and will devote his entire time to clinical pathology.

Philadelphia

University Appointment.—Phyllis A. Bott, Ph.D., has been made professor of physiologic chemistry and chairman of the department at the Woman's Medical College of Pennsylvania. Dr. Bott, a graduate of the University of Wisconsin, Madison, became associate professor at Woman's Medical College in 1941 and in 1946 succeeded Marion Fay, Ph.D., professor of physiologic chemistry, as chairman of the department when Dr. Fay was made dean.

Strittmatter Award.—The Philadelphia County Medical Society has presented its Dr. I. P. Strittmatter Award for 1947 to Dr. Pascal F. Lucchesi "in recognition of his outstanding service to medical education and to the public health in Philadelphia" lately as medical director and superintendent of the Philadelphia General Hospital and formerly as medical director and superintendent of the Philadelphia Hospital for Contagious Diseases. The award, a gold medal and scroll, was made possible through the generosity of Dr. Strittmatter to foster high ideals and distinguished service to the credit of the medical profession in the interest of humanity.

TENNESSEE

Personal.—Dr. John L. McGehee, professor and chief of the division of surgery at the University of Tennessee College of Medicine, Memphis, and surgeon-in-chief at John Gaston Hospital, retired September 1, but will retain his private practice. He has been associated with the university for forty-six years.

Dr. Blassingame Appointed Department Head.—Dr. Charles D. Blassingame, associate professor of otolaryngology since 1934, has been appointed professor and head of the department of otolaryngology at the University of Tennessee College of Medicine, Memphis, succeeding Dr. W. Likely Simpson, who has resigned to devote more time to private practice. Dr. Blassingame is a graduate of Vanderbilt University School of Medicine, Nashville, 1916, and is on the staff of Baptist Memorial Hospital.

TEXAS

Spanish-Speaking Physicans.—Jacob M. Gershberg of New York, president of the International Spanish Speaking Association of Physicians, Inc., was the chief speaker at a banquet in his honor given by the El Paso chapter, September 17. Dr. Gershberg has recently formed new chapters in Juarez, Mexico; Beverly Hills, Calif.; Reno, Nev., and Hot Springs, Ariz., bringing the number of chapters to fifty-nine.

New Postgraduate School at Houston.—The University of Texas' postgraduate school of medicine was established in Houston, September 18, and Dr. Randolph L. Clark Jr., director of the M. D. Anderson Hospital for Cancer Research, Houston, was appointed dean and professor of surgery. The school will ultimately be located in a separate building in the Texas Medical Center. Dr. Clark, a graduate of the Medical College of Virginia, Richmond, in 1932, has been director of the hospital since early in 1947. From 1938-1940 he was on the staff of Mayo Clinic, Rochester, Minn. He was consulting surgeon for the Mississippi State Charity Hospital, Jackson, and Mississippi State Tuberculosis Sanitarium. During the late war, he was chief of the surgical service of the Army Fair Forces Technical Training School.

WEST VIRGINIA

Heart Association Meeting.—The fall meeting of the West Virginia Heart Association will be held at Morgantown October 29. A scientific program will be presented in the afternoon and evening, and a dinner is being arranged in connection with the meeting. Dr. T. Duckett Jones, Boston, will be the principal speaker. Requests for hotel and dinner reservations should be addressed to the secretary, Dr. Fred Richmond, Beckley.

Public Health Appointment.—The division of maternal and child health of the state health department announces the acceptance by Dr. Walter W. Point, Charleston, of appointment as part time obstetrical consultant. He will assist the division in planning the state maternal and child health program. Dr. Point has also been appointed by the public health council as a member of the advisory committee to the division of cancer control of the state health department. He will fill the vacancy caused by the death of Dr. J. Ross Hunter, Charleston.

GENERAL

Postgraduate Medical Assembly.—The International Medical Assembly of the Inter-State Postgraduate Medical Association of North America will meet in the Public Auditorium, Cleveland, November 9-12, under the presidency of Dr. Herman L. Kretschmer, Chicago. A program of diagnostic clinics, addresses and exhibits have been planned. The registration fee is $5.

Premedical Chapter Installed.—The Premedical Club of the University of Miami was recently installed as the Florida Gamma Chapter of Alpha Epsilon Delta, national premedical honor society, an affiliate of the American Association for the Advancement of Science and a member of the Association of College Honor Societies. Alpha Epsilon Delta has about 7,200 members in the forty-seven chapters at colleges throughout the United States.

Announce Urology Award.—The American Urological Association offers an annual award of $1,000 (first prize of $500, second prize $300 and third prize $200) for essays on the result of clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals. The first prize essay will appear on the program of the forthcoming meeting of the association to be held at the Biltmore Hotel, Los Angeles, May 16-19, 1949.

Grants For Vitamin Studies.—The National Vitamin Foundation, 150 Broadway, New York, will award grants-in-aid, totaling $16,000, to Western Reserve University School of Medicine, Cleveland; University of Vermont College of Medicine, Burlington; Massachusetts Institute of Technology, Cambridge, and the University of Southern California School of Medicine, Los Angeles. Among the investigations to be undertaken are the nutritional status of school children, the relationship between pyridoxine (vitamin B_6) and fat metabolism, and the effects of time elements on the utilization of water-soluble vitamins.

Pediatric Conference.—A postgraduate conference in pediatrics will be held November 8-13 at the University of Texas Medical Branch, Galveston, under the auspices of the University of Texas Child Health Program and in cooperation with the Maternal Child Health Division of the Texas State Board of Health. Among the subjects to be discussed are the newborn infant, endocrine disturbances, pediatric psychiatry, pediatric surgery and infectious diseases. Addresses will be given by the University of Texas staff members and the following guest speakers: Drs. Robert L. Jackson, Iowa City; Leo Kanner, Baltimore; J. Cyril Peterson, Nashville, Tenn.; Edith L. Potter, Chicago; Orvar Swenson, Boston, and Lewis K. Sweet, Washington, D. C.

Tuberculosis Association Maintains Culture Bank.—The National Tuberculosis Association reports that since 1946, when its Culture Bank was set up at the Trudeau Laboratory of the Trudeau Sanatorium, Trudeau, N. Y., 384 cultures had been supplied investigators in eighteen foreign countries, twenty-five states and the District of Columbia. Scientists engaged in research are being supplied with standard strains of the tubercle bacillus. Requests for cultures are filled without charge, but investigators are requested to report their research to the National Tuberculosis Association. The laboratory is part of Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Diseases. Recently several strains of streptomycin-resistant tubercle bacilli have been added to the bank. Dr. Edward L. Trudeau, for whom the laboratory is named, is believed to have grown the first culture of the tubercle bacilli in this country, after Robert Koch isolated the germ in 1882. Dr. Trudeau was born one hundred years ago October 5.

Association of Blood Banks Report.—The First Annual Meeting of the American Association of Blood Banks, held in Buffalo, August 26-28, was attended by registrants representing twenty-eight states and six foreign countries. The following officers were elected. Dr. Ralph G. Stillman, New York, president; Dr. Thomas H. Seldon, Rochester, Minn., president-elect; Miss Marjorie Saunders, Dallas, Texas, secretary, and Mr. W. Quinn Jordan, Phoenix, Ariz., treasurer. The officers and directors for the eight districts, into which the country is divided, will constitute the board of directors, which will be the governing policy-making body of the association. Membership in the association is available to ethical, independently operating and policy-making, nonprofit institutions. Associate institutional memberships are also available to hospitals not having a blood bank but interested in blood banking. Individual memberships are open to all persons.

Incidence of Poliomyelitis Declines.—According to the U. S. Public Health Service, a total of 1,699 cases of poliomyelitis was reported during the week ending September 25, as compared with 1,840 (corrected figure) for the preceding week, 881 in 1947 (the five year median) and 1,425 in 1946 for the corresponding week. With a decline of 231 cases, and in view of the lateness of the season, a continued weekly decline may now be expected throughout the remainder of the year. Sharp decreases were reported in the North Central States, especially in Ohio (149 to 58), South Dakota (55 to 23) and Indiana (42 to 25). The incidence declined in California from 326 to 310. The three states which have reported more than than 1,000 cases to date are California (2,982), North Carolina (2,171) and Texas (1,455). The cumulative total to September 25 is 17,653, as compared with 6,498 in 1947, 17,206 in 1946 and a five year median of 8,882 for the corresponding period. Fragmentary data from a few areas indicate, on the basis of a low case-fatality ratio, that the disease has been mild.

Dr. Stanley Awarded Franklin Medal.—Wendell M. Stanley, Ph.D., biochemist of San Francisco, will receive one of the Franklin medals of the Franklin Institute of the State of Pennsylvania "in recognition of his discovery that a virus can be a nucleoprotein rather than a living organism, thereby establishing a significant turning point in virus research; and also of his development of an effective centrifuge-type influenza vaccine by means of which the intensity of future influenza epidemics may be greatly lessened." Dr. Stanley, formerly of the Rockefeller Institute and newly appointed professor and head of the department of biochemistry at the University of California Medical School, Berkeley-San Francisco, and director of the Virus Laboratory of the University of California, received his Ph.D. degree from the University of Illinois, Chicago, 1929, and has been the recipient of a number of awards, including the $1,000 Prize of the American Association for the Advancement of Science in 1936 and the Isaac Adler Prize of the Medical School of Harvard University, 1938; he was Nobel Laureate in Chemistry in 1946.

Nutrition Awards.—The American Institute of Nutrition will make three awards to investigators at its annual meeting next spring. The 1949 award of $1,000 established by Mead Johnson and Company will be given to the laboratory (nonclinical) or clinical research worker in the United States or Canada who has published during 1948 the most meritorious scientific report dealing with the field of the B-complex vitamins. While the award will be given primarily for publication of specific papers, it may be recommended that it be made to a worker for contributions over an extended period. The Borden Award in Nutrition, $1,000 and a gold medal, made available by the Borden Company Foundation, Inc., will be given in recognition of distinctive research by investigators in the United States and Canada which has emphasized the nutritive significance of the components of milk or of dairy products. The award will be made primarily for publication of specific papers. The Osborne and Mendel Award of $1,000, established by the Nutrition Foundation, Inc., for the recognition of outstanding accomplishments in the general field of exploratory research in the science of nutrition, will be given to the investigator who is judged to have made the most significant published contribution in the year. While preference will be given to research workers in the United States and Canada, investigators in other countries are not excluded. Nominations for these awards must be in the hands of the chairman of the nominating committee by Jan. 15, 1949. They should be accompanied by such data relative to the accomplishment of the nominee and his research as will facilitate the task of the committee of judges. Nominating committee chairman for the Mead Johnson Award is Harold H. Williams, Cornell University, Ithaca, N. Y.; for the Borden Award, James M. Orten, Wayne University College of Medicine, Detroit 26, and for the Osborne and Mendel Award, D. W. Woolley, Rockefeller Institute for Medical Research, New York.

Military Surgeons Meeting.—The Association of Military Surgeons of the United States will meet at the Gunter Hotel, San Antonio, Texas, Nov. 11-13, under the presidency of Brig. General Edgar Erskine Hume, Washington, D. C. In addition to addresses by the Surgeons General among others, forum lectures will be given by:

Capt. Harold L. D. Kirkham, U.S.N.R. (Ret.), and Lt. Comdr. S. Baron Hardy, U.S.N.R., Houston, Texas, Military Use of a Cross-Leg Skin Flap.

LeRoy J. Kleinsasser, Dallas, Texas, Subphrenic and Liver Abscesses.

Lt. Col. Kenneth E. Pletcher, Randolph Field, Texas, Movement of the Sick and Wounded by Air.

Capt. Paul E. Spangler, U.S.N., Corpus Christi, Texas, Some Observations on Pilonidal Cyst.

Edward H. Cushing, Washington, D. C., Research in the Veterans Administration.

Edgar J. Poth, Galveston, Texas, Promotion of Healing Following Intestinal Surgery.

Harry Eagle, Bethesda, Md., Chemotherapeutic and Prophylactic Use of Penicillin.

Col. William J. Kennard, Washington, D. C., Aircrew Maintenance: A Problem of Aviation Preventive Medicine.

Lt. Comdr. Philip R. Phillips, U.S.N., Pensacola, Fla., The Psychiatrist in a Dispensary.

Comdr. James G. Bryson Jr., U.S.N., Corpus Christi, Texas, Ocular Manifestations in Intracranial Injury.

C. Ferd Lehmann, San Antonio, Texas, Auto-Sensitization Dermatitis.

Maj. Gen. Charles L. Williams, Bethesda, Md., Control of Murine Typhus Fever.

Col. Rufus L. Holt, Washington, D. C., Progress in Virus and Rickettsial Diseases.

Panel discussions will be given Friday afternoon.

Cancer Symposium at Annual Meeting.—A symposium will be held at the annual meeting of the American Cancer Society, Hotel Commodore, New York, November 6-7. The program is as follows:

The Cancer Problem Today: Charles S. Cameron, New York, A World Problem; John R. Heller Jr., Bethesda, Md., A National Problem; Daniel A. Blain, Washington, D. C., Are There Dangers in Lay Cancer Propaganda?; Herbert L. Lombard, Boston, Creating Awareness.

Treatment—Recent Advances: Bertram V. A. Low-Beer, San Francisco, Diagnosis of Breast Tumors by Radioactive Phosphorus; John H. Lawrence, Berkeley, Calif., Treatment of Diseases of the Hematopoietic System with Artificial Radioactivity; Rulon W. Rawson, New York, Application of Radioactive Materials in the Management of Thyroid Cancer; Norman Treves, New York, Castration as a Therapeutic Agent in Cancer of the Male Breast; Ira T. Nathanson, Boston, Hormone Therapy in Cancer of the Female Breast.

Lung Cancer: Theodore F. Hilbish, Washington, D. C., Results of Community Wide Chest X-Ray Programs in Cancer Case Finding; John R. McDonald, Rochester, Minn., and Peter A. Herbut, Philadelphia, Cytologic Diagnosis of Cancer of the Lung; E. W. Alton Ochsner, New Orleans, Prospects of Improved Control of Lung Cancer.

Cancer Research and Education and the Cancer Problem in General Medical Practice: Harry Eagle, Bethesda, Md., Progress in Cancer Research at the National Cancer Institute; Samuel C. Harvey, New Haven, Conn., Present Status and Future Plans of Cancer Education in Our Medical Schools; Maurice T. Rost, West Hartford, Conn., Cancer Problems of a Family Doctor.

A summary by each chairman will be given at the end of each session, and discussion from the floor will be invited. Speakers at the dinner November 6 will be Dr. L. Henry Garland, San Francisco, "Present Potentials of Radiation Therapy," and Dr. Shields Warren, Washington, "What Can We Expect from Atomic Energy?"

CORRECTION

Dr. Wells at Anderson Hospital.—Dr. Benjamin B. Wells, formerly dean of the University of Arkansas School of Medicine, Little Rock, is director of research and head of the department of clinical pathology at the M. D. Anderson Hospital for Cancer Research at Houston, not at Galveston as was stated in THE JOURNAL, Feb. 21, p. 567. The hospital is a branch of the University of Texas and is the state cancer hospital.

Marriages

MILTON FRANCIS BROWN, Shaker Heights, Ohio, to Miss Ruth Virginia Best at New Brighton, Pa., June 27.

HERBERT MCKELDEN SMITH JR., Staunton, Va., to Miss Anne Noble Sims of Portland, Maine, July 10.

WILLIAM F. KNOFF, Syracuse, N. Y., to Miss Nancy Nettleton Edwards of Casenovia, July 10.

JAMES W. CORRELL, Fairfield, Conn., to Miss Cynthia Cannon Hewitt in New York, August 7.

JOHN GREGG HAND to Miss Irma Virginia Gross, both of Philadelphia, September 4.

SELWYN BRODY to Mrs. Jeanne Davis Carey, both of New York, August 8.

Deaths

John Gordon Wilson ● professor emeritus of otolaryngology at the Northwestern University Medical School in Chicago, died at the Putnam Memorial Hospital in Bennington, Vt., August 13, aged 81, of cerebral hemorrhage. Dr. Wilson was born in Edinburgh, Scotland, Dec. 10, 1866. He received his M.B. and C.M. degrees from the University of Edinburgh Faculty of Medicine in 1890. After studying in Vienna and Berlin he settled in Glasgow, Scotland, where he was appointed surgeon to the Bellahoustin Dispensary and the dispensary of the Victoria Infirmary. In 1901 he accepted the position of instructor in the anatomy department of the University of Chicago and in 1905 became assistant professor of anatomy. In 1908 he joined the faculty of Northwestern University Medical School as professor of otology, in 1924 was named professor of otolaryngology and chairman of the department and in 1945 retired with the rank of professor emeritus. He was a past president and secretary of the Otological Research Committee, past president of the Institute of Medicine of Chicago and the American Otological Society. A specialist certified by the American Board of Otolaryngology, Dr. Wilson was a member of the American Laryngological Association and American Laryngological, Rhinological and Otological Society. He was a fellow of the American College of Surgeons, an honorary member of the Harvey Society of New York, a member of the Illinois State Medical Society, the American Association for the Advancement of Science and the National Research Council. During World War I he served as a captain in the Canadian Expeditionary Forces. He was formerly otolaryngologist on the staffs of the Passavant Memorial and Wesley Memorial hospitals in Chicago. Dr. Wilson was the author of a history of the medical schools of America in the 18th Century, and a medical history of Edinburgh University in the same period as well as of numerous other publications.

Arthur Mullin Wright ● Earleville, Md.; born in Lyndonville, N. Y., in 1879; Cornell University Medical College, New York, 1905; in 1907 joined the faculty of the New York University College of Medicine as assistant in surgery, becoming clinical professor in 1916, associate professor in 1920, George David Stewart professor in 1933 and chairman of the department in 1942; retired in August 1946 with the rank of professor emeritus, after thirty-nine years of teaching; member of the Medical Society of the State of New York, New York Surgical Society, American Surgical Society, International Surgical Association and the New York Academy of Medicine; a fellow and for many years a member of the board of governors of the American College of Surgeons; specialist certified by the American Board of Surgery; an officer in the medical corps of the U. S. Army during World War I, serving as commanding officer of Base Hospital number 1, the Bellevue Unit; later attached to the French Medical Corps, for which service he was made Chevalier of the Legion of Honor of France; interned at St. Vincent's Hospital and from 1912 to 1930 was on its attending staff; for many years director of surgery at the French Hospital; joined Bellevue Hospital in 1907 and in 1927 was made director of the third surgical division, a position he held until his retirement from the hospital; served on the consulting staffs of the Doctors Hospital in New York, Mount Vernon (N. Y.) Hospital, St. Joseph's Hospital in Yonkers, St. Agnes Hospital in White Plains, St. Luke's Hospital in Newburgh, N. Y., and the Central Islip (N. Y.) State Hospital; member of the board of directors of the Union Hospital, Elkton; at a dinner held in his honor in February 1946 by alumni, students and other friends, it was announced that the dais for the auditorium of the New York University-Bellevue Medical Center would bear his name; in 1946 New York University conferred on him the honorary degree of doctor of science; died in New York June 24, aged 68.

Vivean Visscher Wood ● St. Louis; born in Pettis County, Mo., in 1886; Washington University School of Medicine, St. Louis, 1912; assistant professor of otolaryngology at St. Louis University School of Medicine; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Oto-Laryngology, American Laryngological Association, American Laryngological, Rhinological and Otological Society and the American Otological Society; fellow of the American College of Surgeons; served during World War I; on the staffs of the Jewish, Bethesda, De Paul and St. Luke's hospitals and Deaconess Home and Hospital; consulting otolaryngologist at St. Mary's Group of Hospitals; died in University City, Mo., June 20, aged 61, of heart disease.

Walter John Farrell ● Johnson City, N. Y.; born in Chicago in 1890; Fordham University School of Medicine, New York, 1917; also a graduate in pharmacy; past president of the Broome County Medical Society; member of the American Public Health Association, New York State Health Officers Association and the Association of Military Surgeons of the United States; for many years health officer and school physician; served during World War I; on the consulting staffs of the Ideal Hospital in Endicott, N. Y., and Binghamton (N. Y.) City Hospital; affiliated with Our Lady of Lourdes Memorial Hospital in Binghamton, N. Y., and the Charles S. Wilson Memorial Hospital, where he died July 25, aged 57, of mesenteric thrombosis.

Marshall Clark Keith, Cheyenne, Wyo.; born in Carrol County, Ill., April 12, 1874; Rush Medical College, Chicago, 1896; member of the American Medical Association; for many years secretary of the Wyoming State Medical Society; formerly secretary of the Wyoming State Board of Medical Examiners and secretary and state health officer of the Wyoming Department of Public Health; for many years treasurer of the school board; served as county physician; scientific editor of the Wyoming Section of *Colorado Medicine;* author of a book of poems; affiliated with Natrona County Memorial Hospital, where he died in July, aged 74, of uremia.

Augustus William Anderson, New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1943; served during World War II; formerly an intern and resident in orthopedics at the Charity Hospital, where he died July 21, aged 29, of brain tumor.

Herbert Aaron Citron, Newport, Ky.; University of Cincinnati College of Medicine, 1948; interned at the Michael Reese Hospital in Chicago; died in the Children's Hospital, Boston, July 6, aged 23, of Hodgkin's disease.

George Ingersoll Dakin, Grosse Pointe, Mich.; Michigan College of Medicine and Surgery, Detroit, 1891; died in Alexander Blain Hospital, Detroit, July 21, aged 78, of cerebral hemorrhage.

Perry Cleveland Farnell, Branford, Fla.; Medical College of the State of South Carolina, Charleston, 1912; member of the American Medical Association; died June 5, aged 63, of coronary occlusion.

Karl L. Fife, Lordsburg, N. M.; University of Colorado School of Medicine, Denver, 1935; served overseas during World War II; on the staff of the Lordsburg Hospital; died May 23, aged 45, in a glider crash.

James Surran Fleming ● Memphis, Tenn.; University of Tennessee College of Medicine, Memphis, 1913; served in France during World War I; past president of the Memphis Urologic Society; died July 6, aged 57.

Frederick Biggers Fox, Freeburg, Ill.; St. Louis University School of Medicine, 1906; died in St. Elizabeth's Hospital, Belleville, July 21, aged 76, of cerebral hemorrhage.

Michael Leo Gallagher, Oak Park, Ill.; Rush Medical College, Chicago, 1899; served on the staffs of various Veterans Administration hospitals; died at Downey July 14, aged 79, of coronary occlusion.

Frank Hackett Gilreath, Lexington, Va.; University of Nashville (Tenn.) Medical Department, 1898; member of the American Medical Association and the Medical Society of the State of North Carolina; died June 19, aged 79, of cardiovascular disease.

Nathan Bernard Glassman ● Boston; College of Physicians and Surgeons, Boston, 1916; died June 8, aged 58, of agnogenic myeloid metaplasia.

Victor Maurice Gore ● Tucson, Ariz.; Washington University School of Medicine, St. Louis, 1908; member of the founders group of the American Board of Surgery; fellow of the American College of Surgeons; affiliated with the Pima County General Hospital and the St. Mary's Hospital and Sanatorium, where he died May 30, aged 63, following gastric resection for peptic ulcer.

William C. Kiser, Vale, N. C.; Southern Medical College, Atlanta, 1889; died June 20, aged 81, of heart disease.

George Albert Landes, Parsons, Kan.; Rush Medical College, Chicago, 1904; member of the American Medical Association; served during World War I; affiliated with Mercy Hospital; died June 24, aged 67, of coronary heart disease.

William Polk Longmire Sr. ● Sapulpa, Okla.; Hospital College of Medicine, Louisville, 1904; formerly affiliated with the Indian Service; fellow of the American College of Surgeons; on the associate staff, Morningside Hospital, Tulsa, and consulting staff, St. John's Hospital, Tulsa; on the staff of City Hospital, where he died June 1, aged 66, of heart disease.

V 1
194

Hector John MacLean, Boston; Baltimore Medical College, 1908; affiliated with Massachusetts General Hospital and Massachusetts Memorial Hospital, where he died June 21, aged 72, of heart disease.

Jodia A. Magraw, Gilman City, Mo.; Lincoln (Neb.) Medical College of Cotner University, 1899; died in Macon June 18, aged 88.

Frank C. Makepeace, Hackensack, N. J.; Kentucky School of Medicine, Louisville, 1906; formerly associated with the U. S. Public Health Service; died June 28, aged 65.

Nathaniel Robert Mason, North Conway, N. H.; Harvard Medical School, Boston, 1901; member of the American Medical Association, Massachusetts Medical Society and the New England Obstetrical and Gynecological Society; fellow of the American College of Surgeons; affiliated with Massachusetts General Hospital and Boston City Hospital, where he died May 3, aged 72, of hypertension and arteriosclerotic heart disease.

Willard Grant McDade, East Liverpool, Ohio; Ohio Medical University, Columbus, 1905; died May 8, aged 75.

Alexander H. McLeod ● Aberdeen, N. C.; Baltimore Medical College, 1896; died June 19, aged 77.

Fraley F. McMillan, Charlevoix, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1906; member of the American Medical Association; served as county coroner; affiliated with Charlevoix Hospital, where he died June 29, aged 66, of coronary occlusion and myocardial infarction.

Charles A. A. J. Miller, Baltimore; Baltimore University School of Medicine, 1892; formerly assistant superintendent of Baltimore public schools; died in Union Memorial Hospital July 4, aged 88, of gastric and prostatic hemorrhage.

Albert Frederick Miller, Auburn, N. Y.; Syracuse University College of Medicine, 1897; died in St. Petersburg, Fla., June 17, aged 74.

Aston Hugh Morgan, Wilkes-Barre, Pa.; College of Physicians and Surgeons, Baltimore, 1891; member of the American Medical Association; died May 27, aged 90, of hypostatic pneumonia and arteriosclerosis.

James H. Morrison, Hartsville, Ind.; Kentucky School of Medicine, Louisville, 1893; served as county health commissioner; died in Memorial Hospital, Greensburg, June 29, aged 81, of cerebral hemorrhage.

Joseph Aloysius Mullen, Houston, Texas; Jefferson Medical College of Philadelphia, 1893; member of the American Medical Association; fellow of the American College of Surgeons; died in St. Joseph's Infirmary June, aged 81, of bronchopneumonia.

Lewis James Muthart, Jermyn, Pa.; Jefferson Medical College of Philadelphia, 1906; died May 12, aged 66, of carcinoma of the right lung.

John Trimble Palmer ● Pine Bluff, Ark.; Medical Department of Tulane University of Louisiana, New Orleans, 1905; for two terms served on the state examining board; died in Davis Hospital May 25, aged 69, of coronary occlusion.

Meyer Paretzky ● Huntington Park, Calif.; University of Kharkov Faculty of Medicine, Russia, 1917; member of the American Trudeau Society; for many years chest clinician for the Los Angeles City and Los Angeles County health departments; member of the tuberculosis division of the Los Angeles General Hospital; died May 17, aged 53.

William O. Phillips, Newburgh, Ind.; Pulte Medical College, Homeopathic, Cincinnati, 1900; served during World War I; major, medical reserve corps, not on active duty; died in Altadena, Calif., May 20, aged 69, of carcinoma of the common bile duct.

Charles Felix Prairie ● Massena, N. Y.; Syracuse University College of Medicine, 1906; secretary and past president of the St. Lawrence County Medical Society; served during World War I; president of the board of education; president of the Massena National Bank; on the staff of the Massena (N. Y.) Memorial Hospital and the A. Barton Hepburn Hospital in Ogdensburg, where he died June 30, aged 63, of carcinoma of the lower esophagus.

Julian McGruder Robinson, Danville, Va.; University College of Medicine, Richmond, 1899; member of the American Medical Association and the Southern Surgical Association; fellow of the American College of Surgeons; affiliated with Memorial Hospital; died June 28, aged 73.

Thomas Bell Rodham, Scranton, Pa.; Medico-Chirurgical College of Philadelphia, 1897; died June 15, aged 80, of cerebral hemorrhage.

John Christian Serkland, Rothsay, Minn.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1900; member of the American Medical Association; served on the board of education and as health officer and mayor of Rothsay; affiliated with St. Luke's Hospital in Fargo, N. D., where he died May 9, aged 75, of coronary thrombosis.

Eubert Verner Simons, Spring Valley, Minn.; Keokuk (Ia.) Medical College, College of Physicians and Surgeons, 1902; died May 27, aged 74, of cardiac failure.

Samuel Alexander Springwater ● Los Angeles; Memphis (Tenn.) Hospital Medical College, 1894; member of the Illinois State Medical Society; died May 14, aged 78.

Lawrence Lorraine Stepp ● Fort Lauderdale, Fla.; University of Pennsylvania School of Medicine, Philadelphia, 1917; died May 30, aged 56, of carcinoma of the lung.

Irl Thomas, Ashland, Ky.; Vanderbilt University School of Medicine, Nashville, Tenn., 1915; member of the American Medical Association; for many years affiliated with the Veterans Administration, serving on the staffs of various Veterans Administration hospitals; died in the Veterans Administration Hospital, Louisville, June 21, aged 56.

Louis Monroe Tomlinson ● Harveyville, Kan.; Kansas Medical College, Medical Department of Washburn College, Topeka, 1913; past president of the Wabaunsee County Medical Society; served overseas during World War I; died in Topeka, July 1, aged 59.

Mark La France Underwood, Little Rock, Ark.; Marion-Sims College of Medicine, St. Louis, 1898; served on the staff of the State Hospital; died May 29, aged 72, of congestive heart failure.

George Edgar Vaughan, Winnebago, Minn.; College of Physicians and Surgeons of Chicago, 1895; died in Rochester, Minn., May 31, aged 83, of calcareous aortic stenosis and hypertrophy of the prostate.

James R. Vermillion, Princeton, W. Va.; Maryland Medical College, Baltimore, 1900; member of the American Medical Association; died June 20, aged 76, of arteriosclerosis.

Jay Herbert Wallahan, Corning, Iowa; St. Louis College of Physicians and Surgeons, 1897; member of the American Medical Association; died June 4, aged 82, of cerebral hemorrhage.

Edward J. Weitenberner, Detroit; Detroit College of Medicine, 1899; died June 25, aged 71.

Francis M. Wilmer, Winfield, Kan.; College of Physicians and Surgeons of Chicago, 1896; member of the American Medical Association; died June 22, aged 77.

William David Wolfe ● Baltimore; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1934; specialist certified by the American Board of Dermatology and Syphilology; member of the American Academy of Dermatology and Syphilology; served in New Guinea and the Philippines during World War II; affiliated with South Baltimore General and Johns Hopkins hospitals; died in Sinai Hospital June 29, aged 37, of acute monocytic leukemia.

William Vincent Woods ● Indianapolis; Indiana University School of Medicine, Indianapolis, 1929; associate professor of orthopedic surgery at his alma mater; specialist certified by the American Board of Orthopaedic Surgery, Inc.; attending orthopedic surgeon to Methodist, St. Francis and St. Vincent's hospitals; died June 3, aged 45, of coronary thrombosis.

Edwin Sayre Woodyard, Pennsboro, W. Va.; Medical College of Virginia, Richmond, 1925; served in France during World War I; died June 14, aged 50, of coronary thrombosis.

Charles Clinton Yarbrough, Memphis, Tenn.; Tennessee Medical College, Knoxville, 1893; vice president of the Wayne County (Mich.) Medical Society in 1901 and 1902; died in the Memphis Eye, Ear, Nose and Throat Hospital June 11, aged 79, of cerebral hemorrhage.

Joseph R. Zicarelli, New York; Long Island College Hospital, Brooklyn, 1909; member of the American Medical Association; affiliated with New York Eye and Ear Infirmary, New York Post-Graduate Hospital and St. Vincent's Hospital, where he died June 28, aged 65.

Edgar Nelson Zinn ● Fort Dodge, Iowa; Chicago College of Medicine and Surgery, 1909; also a graduate in pharmacy; past president of the Webster County Medical Society; affiliated with St. Joseph Mercy Hospital, where he died May 29, aged 61, of carcinoma of the colon.

Foreign Letters

LONDON

(From Our Regular Correspondent)

Sept. 11, 1948.

The Uses of Health Centers

The proposed "health centers" promise to be a useful innovation in the scheme of the National Health Service. The British Medical Association has published an important report on the subject by a special committee appointed by the Council to investigate existing forms of group practice and other forms of collaboration between general practitioners, and to relate this and other experience to development of health centers. The report points out the great importance of the family doctor, to whom the patient generally resorts in the first instance. This relationship is strongest in the rural areas and in towns with a stable population and weakest in the dormitory suburbs of London. In recent years there has been a partial breakdown in the family doctor system. People make direct use of the various kinds of special clinics established everywhere by the local authorities. These have no organized contact with the general practitioner, and their work overlaps with his considerably. Inefficiencies arise when treatment is given to the same patient at different times by different doctors. The family doctors, preoccupied with the individual, were slow in realizing the importance of preventive work. Also the doctor's fee prevented people from seeking advice early for minor ailments. The solution was the establishment by the local authorities of free clinics with preventive functions, such as those for antenatal care. Single-handed practice, which, except for partnerships, is almost universal, has many disadvantages. The doctor is on call twenty-four hours a day and for seven days a week. He has difficulty in getting away for postgraduate study. He does not enjoy the advantage and stimulus of daily consultation and discussion of cases with his colleagues.

The Council holds that cooperation of general practitioners in groups, with a partial differentiation of function, is the most effective way for them to cover the whole field of family practice while preserving the personal relationship between physician and patient. Also some way must be found of uniting the work of family practice with that of the clinics. The health center concept includes a well equipped building housing a group of doctors who perform in a coordinated way all the work now done by general practitioners and clinic medical officers. These doctors should have an organized association with the work of the local hospital. Also the center should unite general practitioners' services with the services of the local health authority. The center should have its own staff of nurses and midwives, so that frequent consultations will coordinate the work of doctors and nurses. The provision of specialist services in relation to health services is under consideration and will be discussed in a final report.

Many medical schools are taking an interest in the possibility of medical students' or new graduates' gaining experience of general practice and social medicine in health centers under the guidance of experienced general practitioners. The association has in a previous report drawn attention to the defects of clinical training based entirely on special hospitals. The Council agrees that the health center should take a valuable part in medical education.

With regard to the population to be served by one health center, it is estimated that 8 doctors would be about the average employed. These could serve a population of 25,000 in an urban district. This would cover a radius of one mile from the center. But the district of a center should not be rigidly defined, as this would limit the public's choice of doctor. A person should not be compelled to go to the nearest center if he prefers to go farther for a doctor of his choice.

A Textbook Invasion

In some ways this country has not recovered from the effects of the war as well as Belgium and Holland in spite of the disadvantage of German occupation. The obvious explanation is that in addition to recovering from the war they had not to bear the strain of a political and economic revolution. Britain should have been allowed to recover from the war before she was submitted to the socialistic experiment. The result is that the inflation, due to the war, has increased and shortages threaten to become permanent. Paper shortage, for example, has curtailed newspapers and rendered the publication of books difficult. A survey of the supply of textbooks required by Cambridge undergraduates was recently made by the Association of Scientific Workers. It has led to the statement in the press that the modern English library, in all branches of science, is rapidly becoming an American one. Nearly half the scientific books that the average student is required to buy are not available. American books cover 33 per cent of the books bought against 10 per cent before the war. While it is recognized that many American books are invaluable, the demand has been made, since we already give priority to the importation of scientific books, that a similar priority should be given at home in the allocation of paper supplies. Figures have not been given separately for medical books, but the shortage of British medical books, though undoubtedly felt, is not so great as that of scientific books.

Artificial Insemination Condemned by Archbishop's Committee

A recommendation that artificial insemination in human beings, involving the use of any donor other than the husband, should be made a criminal offence is made in a report by a commission set up by the Archbishop of Canterbury "to consider the practice of human artificial insemination with special reference to its theological, moral, social, psychological and legal implications. The Bishop of London was chairman of the committee, which included six doctors. The report is not a church document, nor is it addressed to the general public. It is meant to assist doctors, lawyers and theologians who have in their several professions to consider the implication of the practice.

Of the four findings one was unanimous, that "assisted insemination between husband and wife may be justified." All but one member agreed that when a donor was involved other than the husband insemination was wrong and contrary to Christian standards. All but one also agreed on the necessity for legislation. In praise of doctors who supplied evidence to the commission the report states: "In every case they are persons of the utmost sincerity, impelled by a genuine compassion for those who are victims of sterility and by a deep desire to help them." The report discusses the history of the rubject, its psychologic aspects, legal, sociologic and eugenic implications, a theological implication and conclusions.

Journal Ceases Publication Because of the Costs

The increasing cost of production have led to the cessation of publication of a valuable periodical, the *Liverpool Medico-Chirurgical Journal*, which was founded in 1881 as the *Journal of the Liverpool Medical Institution*. It has been decided that all papers and addresses read before the Institution shall be permanently recorded by filing typewritten copies in the library.

In a foreword to the last number the Council justly says that much erudition and medical knowledge has been advanced through the journal and expresses the hope that one day economic conditions will be more favorable for its resumption. This cessation of publication is one example of the folly of the persistent trade union policy of forcing up wages, with no increase of output but rather a diminution, which has flourished under the labor Government. The consequence is that the purchasing power of money has declined by more than a half.

ITALY

(From Our Regular Correspondent)

Florence, July 31, 1948.

Macrocytic Hyperchromic Anemias

At the eighth congress of the Italian Hematologic Society in Turin, Professor Fausto Penati reported on "Systematization of the Macrocytic Hyperchromic Anemias." Those anemias are considered as hyperchromic in which the average contents of hemoglobin of the red blood corpuscles are superior to the average normal value. Those anemias must be considered as macrocytic in which the average globular volume is superior to the normal. When not indicated explicity, the term macrocytosis should refer to the volume and not to the diameter, because the two do not always show a parallel behavior. The term megalocytosis has not a particular value except for indicating a particularly conspicuous degree of macrocytosis. In discussing the relation between macrocytosis and hyperchromemia, the speaker emphasized that in mammals the relation between hemoglobin and globular volume is constant. On the contrary, the hemoglobin concentration is not constant and has a tendency to decrease with the reduction of the volumetric values according to a parabolic curve. The dimensions of the mature red blood corpuscles depend on those of the erythroblasts from which they are developed. If they develop from erythroblasts above the norm, the erythrocytes will have a volume and, generally, a content of hemoglobin above the norm.

With regard to the pathogenesis of hyperchromic macrocytosis Professor Penati distinguished various mechanisms which may cause it: 1. Hyperchromic macrocytosis of megaloblastic erythropoiesis due to lack of action of the antipernicious factor. With the discovery of folic acid new ways have opened up to clarify the mechanism of this type of anemia. So far the relationship between the hepatic and the folic acid factor has remained obscure, and the innermost significance of megaloblastosis likewise is obscure. 2. Hyperchromic macrocytosis of megaloplastic erythropoiesis by hyperplasia and reticulohistiocyte dysplasia. In a series of diseases definitely distinct from pernicious anemia (erythremic myelosis, aplastic leukemia, hemolytic splenomegaly) one may observe medullary megaloplastosis without the possibility of admitting an association with pernicious anemia. Anemias of that type are hepatoresistant. Also in these anemias there is a hyperplasia or reticulohistiocyte dysplasia, as in the hyperchromic macrocytoses. In these cases one must admit an atypical formation of erythroblastic tissue under the aspect of hyperplasia and reticulohistiocyte dysplasia. 3. Hyperchromic macrocytosis of erythropoietic inhibition. In conditions of myeloid inhibition there may be phenomena of inhibition of the processes of proliferation with an activity of more immature erythroblastic elements from which macrocytes develop. 4. Hyperchromic macrocytosis of macroblastic stimulation. In conditions of pathologic stimulation or of compensation, one must admit the possibility that the stimulus is exerted predominantly on the more immature erythroblasts with macrocytosis as a sequela. 5. Macrocytosis resulting from reticulocytosis. An increase in the average globular volume may be determined by pronounced reticulocytosis; in such circumstances there is not a parallel rise of the globular value. 6. Macrocytosis resulting from spherocytosis. According to Professor Penati, there is no justification for speaking of macrocytosis due to spherocytosis in the absence of elements suggesting that the spherocytes might be of a volume superior to the norm. 7. Macrocytosis by means of alteration. Some authors consider the possibility that by variation of the protein concentration of plasma there may occur a swelling of the red blood corpuscles with an increase in the average globular volume. This concept has not been proved.

Since these various forms may be associated with one another the speaker presented his own classification based on criteria partly pathogenic and partly clinicomorphologic. The macrocytic hyperchromic anemias thus have been divided in two categories: that of megaloblastic type or the group of pernicious anemias, and that of macroblastic type, which comprises three subgroups: those from myelotoxic erythropoietic inhibition, those of macroerythroblastosis of erythropoietic stimulation and those associated with hemolytic and myelotoxic factors. Between these categories may be placed the anemias of pernicious type because their morphologic character does not correspond with an analogous pathogenetic mechanism and which therefore are typically hepatoresistant.

THE NETHERLANDS

(From Our Regular Correspondent)

Aug. 25, 1948.

Dr. Morris Fishbein in Amsterdam

The *Nederlandsch Tijdschrift voor Geneeskunde*, leading Dutch medical journal, publishes a front page article by the president of the board of editors, Professor van Loghem, on the recent visit of Dr. Morris Fishbein. It speaks highly of Dr. Fishbein's profound interest in the history of medicine and his first hand knowledge of present day problems.

The *Tijdschrift* gave a dinner in the Park Hotel for its guest of honor and Mrs. Fishbein, which was attended by the editors, the president and the secretary of the Netherlands Medical Association, the chief medical inspector, members of the faculties of Amsterdam, Leyde and Utrecht, and other representatives of the medical profession. Most of them had visited the United States after the war on grants from either the Rockefeller Foundation or the Dutch Government. Among them were Prof. Woerdeman, chief editor of *Excerpta Medica*, Prof. Jansen, exchange professor to Toronto, Prof. Swellengrebel, who was recently awarded the Walter Reed medal on the occasion of the Malaria Congress at Washington.

Prof. van Loghem was in the chair and in his word of welcome explained that Holland is on her way to the excellent prewar figures of general mortality, tuberculosis and infant mortality as a result of the cooperation of the governmental services and private health institutions, especially the "Cross" societies.

Dr. Fishbein gave an address on actual problems in which he was especially interested and afterward stimulated useful discussions. Responding to an invitation of the chairman, Dr. Heynsius van den Berg gave a talk on experience with BCG in Holland. Other speakers were Dr. Banning, chief medical inspector (The Hague), Prof. Holmer (of Leyde University), and Prof. Heringa, rector of the University of Amsterdam and president of the Students Sanatorium at Laren, which Dr. Fishbein had honored by a visit in the afternoon.

Prof. Charlotte Ruys, who will preside at the Philadelphia congress of the International Association of Women Doctors in 1950, expressed the deeply felt gratitude of those present, who nearly all had received hospitality, help and friendship in America.

DENMARK

(From Our Regular Correspondent)

COPENHAGEN, Sept. 9, 1948.

The Teaching of the History of Medicine

How profoundly ignorant we all were of the history of medicine when we passed our final examinations! And what a boon it would have been if from the outset we had been equipped with that perspective and sense of proportion which only a solid grounding in this subject can give! We would have learned that what successive generations of physicians have hailed as epoch-making discoveries have been dismissed later as trifles or even as fallacies. These reflections must have been in the minds of the men who, under the auspices of the Danish manufacturing chemists, have started the publication of a new periodical, *Medicinsk Forum*. This gift to every Danish physician and chemist must not be regarded as a sly attempt on the part of wholesale manufacturing chemists to push their wares under the guise of scientific publications. This new periodical, which is to appear ten times a year, contains no advertisements. One of its editors, Dr. E. Jacobsen, is responsible for the modern side of medicine, while his co-editor, Dr. E. Gotfredsen, deals with its history. In a series of articles on the reception given to great discoveries in medicine, the reader is shown how thorny is the path of the pioneer (witness the fate of Semmelweiss in connection with puerperal fever). The discovery of the stethoscope was given a more appreciative greeting and the Danes, at any rate, were quick to honor its discoverer.

The Early Treatment of Mental Disease

Dr. H. I. Schou, whose association with the Dianalund Sanatorium for Nervous Ailments has helped make his well deserved standing in Denmark as a psychiatrist, has lately made a forceful appeal to his countrymen to face what he bluntly calls a scandal. It concerns the neglect of the early rational treatment of light psychoses whose victims are neglected till they have become incurable. He is at present engaged on a statistical study of the costs to the community in 1944 and 1946 of the so-called nervous ailments. Though his study is not completed, he has already come to the conclusion that these ailments are more costly than cancer, tuberculosis, rheumatism or infantile paralysis. At present the Dianalund Sanatorium is the only institution of its kind in Denmark which provides for the treatment of incipient mental disease. With its 115 beds, it is incapable of satisfying all the needs of a country with a population of 4,500,000. To be sure, there are various other hospitals and asylums for which annexes are at present being planned for the "open" care of borderland cases of mental disease, but, with the housing problem in its present phase, the obstacles to the realization of all these plans are indeed great. What makes the situation tantalizing is that, according to Dr. Schou, between 75 and 85 per cent of all the cases of periodic depression can be cured by shock treatment in two to three months if taken in time, whereas when neglected such depression will last three to six months.

Mental Hygiene

The National Mental Hygiene Association has begun to publish a journal. The first number contains an article on "The Risk of Insanity in Denmark," in which Dr. K. H. Fremming gives a summary of a study which he has recently made of the population of the island of Bornholm. This study, carried out in the period 1938-1945, deals with the 5,500 persons who were born in Bornholm in the eighteen eighties. At the time of this investigation, all the survivors of this group were over the age of 50 and were therefore more or less beyond the range of hereditary mental diseases. Dr. Fremming found that up to the age of about 55 in 4 per cent of this cross section of a Danish community mental disease had developed. Schizophrenia accounted for 0.9 per cent and the manic-depressive diseases between 1 and 2 per cent, women in this category being twice as numerous as men. Epilepsy and mental disease due to syphilis were about equally frequent, in each case affecting 3 out of every thousand persons. About 1 per cent of the population suffered from "psychogenic" mental disease mainly due to extraneous circumstances. More than 1 per cent were mentally defective, and at least 3 per cent were psychopathic. In other words, in the whole of Denmark there are, according to Dr. Fremming, at least 120,000 psychopathic and about 100,000 neurasthenic persons. In this last category women outnumber men in the ratio of 15 to 10. When all these categories are run into one, it will be seen that about 12 per cent of Danes are psychically abnormal or are, or have been, insane. According to a pamphlet recently issued by the National Mental Hygiene Association, every third hospital bed in Denmark is devoted to mental disease. In addition to the 11,000 mental patients in hospitals there are some 14,000 insane patients not in hospitals and some 16,000 who at some time or other have been insane. With these and other impressive statistics, the National Association appeals to the public for funds and other help in making better provision for the organized prevention and treatment of mental disease throughout Denmark.

The Clothing of Asylum Patients

The Journal of the Danish Medical Association has printed an exchange of views on the subject of the clothing of patients in asylums. A correspondent complains that the uniforms with which an asylum equips its patients make them look like a cross between a clown and a convict. How can they avoid an inferiority complex in this apparel when their friends come to visit them? Another correspondent, representing the authorities responsible for this state of affairs, defends it with the rather meager plea that plans for the reform of the clothing of lunatics in asylums "will be realized as soon as the clothing situation permits."

BRAZIL

(From Our Regular Correspondent)

RIO DE JANEIRO, Sept. 6, 1948.

The Rh Factor in Brazilian Cities

Drs. Mario P. de Mesquita and Vera Leite Ribeiro, of the blood bank of the Fernandes Figueira Pediatric Hospital, published a paper about the hematology of the Rio de Janeiro population, some of which have been reported in previous letters. The new paper deals with sensitization by the Rh factor and the etiology of fetal erythroblastosis. By immunizing guinea pigs with subcutaneous injections of pure stroma of red blood cells of Rhesus monkeys (Macaca mulatta), the writers were able to produce potent agglutinating Rh serums, proving, it appears, that the main fraction of the Rh antigen is found in the cellular stroma itself. Accordingly, the hypothesis of the exclusive passage of whole red cells through the placental barrier which has been frequently advanced to explain the production of Rh agglutinins seems unnecessary. To do this, the erythrocytes were separated, washed in isotonic sodium chloride solution and lysed in double distilled water. The stroma thus obtained was repeatedly washed until the supernatant fluid did not show any trace of albumin detectable by the Heller ring test and until the smears, prepared with the sediment and stained by the May-Grünwald-Giemsa method, did not reveal any complete red cell when examined microscopically under 1,500 diameter magnification.

The second part of the paper dealt with the immunization of guinea pigs to yield Rh antibodies; Drs. Mesquita and Ribeiro report a new technic. The inactivated serums of 25 normal adult guinea pigs, diluted to 1 to 4, was used for the agglutinating tests with 2 per cent suspensions of rhesus red cells in final dilutions from 1 to 5 to 1 to 80. The citrated blood of the monkeys was first filtrated through sterilized gauze to retain the clots, if any, and then centrifuged and washed, the centrifugation and washing being repeated several times. After each centrifugation the separated red cells were mixed with

more isotonic sodium chloride solution and transferred to another tube, the sediment containing some stroma and broken red cells being abandoned in the first tube. The washing of the red cells was continued until the supernatant fluid did not show the slightest trace of albumin. By this technic, a much higher sensibility of Rh agglutinins was disclosed at 5 C. than at 37 C., which confirms the previous findings of Diamond and Abelson. In addition, absorption tests disclosed that such enhanced sensitiveness derives fundamentally from specific properties of Rh agglutinins and not from a nonspecific cold agglutination. The production of serum by the new technic is still under study before its utilization for diagnostic purposes.

While still using serums of American manufacture, the writers reported that among 220 white adults, Brazilian-born residents of Rio de Janeiro selected for blood donors at the Fernandes Figueira Hospital, the Rh factor reaction was negative in 28, or 13.2 per cent. Previous results reported recently in Brazil in similar conditions by Ottensooner and Pasqualini (São Paulo, 1934, 47 examinations), by Lacaz, Ferreira, Malone and Yahn (Rio de Janeiro, 1946, 445 examinations), again by Ottensooner and Pasqualini (São Paulo, 1947, 191 examinations) and by the present writers (Rio de Janeiro, 1947, 212 examinations) had shown negative percentages of 15.0, 14.2, 14.7 and 13.2, respectively, which gives the general average negative rate of 13.93 per cent for the combined sample of 1,115 persons from the two greatest cities of Brazil.

Treatment in 300 Cases of Tetanus

Dr. Joaquim M. Fonseca is head of a department of São Francisco de Assis Hospital, where most cases of tetanus of this city are treated. Since 1925, Dr. Fonseca has attended 300 cases of tetanus. He recently reviewed at the National Academy of Medicine the results of treatment. With more use of the specific therapy, the results began to improve, from year to year, so much so that at present 83 per cent of the patients are cured. According to the point of entrance of the infection, Dr. Fonseca classifies as "severe" the cases of tetanus of the hand, the throat, the uterus and the umbilicus and those connected with the puerperal state, particularly the ones following induced abortion. The routine treatment is based on the early use of the specific therapy with a dosage of 5,000 American units for adult and 3,000 for children.

Number of Physicians in Brazil

A recent publication of the Bureau of National Statistics disclosed the number of physicians in Brazil. According to the 1946 figures, there is an average of one physician to 2,780 inhabitants. The worst situation is that of the states of Maranhão, Piauhy and Parahiba, which had less than one physician for 10,000 inhabitants. Of the 16,939 physicians engaged in professional activity in the whole country, 60.4 per cent were in the twenty largest cities with an aggregate population of more than 6,000,000. Out of 10,235 physicians practicing in the twenty largest cities, 6,264 worked in the cities of Rio de Janeiro and São Paulo, with an aggregate population of more than 3,700,000.

Dr. J. Bruno Lobo

In the last five years Dr. J. Bruno Lobo has been the radiologist of the Department of Gynecology of Rio de Janeiro University. Toward the beginning of last year he began to feel the early symptoms of radiodermatitis of the feet. With the aggravation of the illness, the case was definitively diagnosed as one of radiodermatitis. An American specialist suggested to Dr. Lobo that he go to the United States, where treatment of the disease could be done with great hope of success. But the trip and the treatment involve great expenditure of money, which young Dr. Lobo is unable to afford. The case became news through reports in the press, arousing public interest so much that the Brazilian Congress is passing legislation to appropriate the sum needed by Dr. Lobo for his treatment.

Correspondence

NEUROGENIC BLADDER OF POLIOMYELITIS

To the Editor:—In the Aug. 14, 1948 issue of THE JOURNAL under "Current Medical Literature" on page 1485 is abstracted an article by W. L. Valk from the *Kansas Medical Society Journal* (49:193-136 [March] 1948), entitled "Neurogenic Bladder of Poliomyelitis." The author stated that cystometric studies on patients with this disease made during the study of poliomyelitis seen at the University of Kansas Medical Center during the 1946 epidemic had convinced him that a type of neurogenic bladder is produced by the disease and that this communication represents the first description of cystometric studies of the neurogenic bladder of poliomyelitis.

In the *Journal of Urology* for June 1936, I published a paper entitled "Urinary Complications In An Epidemic of Poliomyelitis" from the School of Medicine of the University of Southern California and the Urological Department of the Los Angeles General Hospital, based on a study of the epidemic of 1933-1934 in Los Angeles County, in which there were 1,792 cases with a positive diagnosis of poliomyelitis. Eighty per cent of these patients were hospitalized, more than half of them in the early systemic phase of the disease. The incidence of urinary complications was unusually high, and many cystometric studies were made, typical examples of which appear in the paper. Whether or not these were the first cystometrograms made for patients with poliomyelitis presenting symptoms of a neurogenic bladder is not definitely known, but certainly they antedated the work of Dr. Valk.

BURNETT W. WRIGHT, M.D., Nashville, Tenn.

FATAL REACTIONS AFTER AMINOPHYLLINE

To the Editor:—I read with great concern the article by Drs. Bresnick, Woodard and Sageman, THE JOURNAL, February 7, page 397, regarding fatal reactions following intravenous administration of aminophylline, and a letter on the subject by Dr. Harold Thomas Hyman in the issue of March 27, page 895. The latter believes that "the deaths are more likely explicable on the basis of 'speed shock.'" The clinicians who do a number of intravenous injections and see them being done have, certainly, a claim to have their say in the matter. I am firmly of opinion that the importance of speed shock in bringing about intravenous fatalities has been unduly exaggerated. Consider the thousands of intravenous injections given by doctors all over the world with rarely a watch before them! In India I have seen intravenous injections in a big hospital given by illiterate ward boys without a watch in their pocket. Their speed of injection can be imagined from their keen desire to finish the work speedily. Yet no fatality due to intravenous injection has ever occurred there! With due deference to all concerned, I may be allowed to say that speed shock is one of the myths that have been introduced in medicine by ambitious workers. Speed atrocities in intravenous administration must be in enormous numbers per day compared with the fatalities that are known to follow. By this, I do not desire to minimize the importance of speed in intravenous injections. Speed may cause a fatality by its effect on a weak and degenerated myocardium. But ordinarily the speed of an intravenous injection, due to the average bore of the needle used, is not of such a magnitude as to occasion death in a person whose myocardium is not too bad.

A remarkable point in these fatalities is that only certain drugs, like the mercurial diuretics and arsenicals, are notoriously associated with them. This leads one to presume that there is

something in the nature of drugs rather than in the mode of administration that is responsible for death.

Immediate deaths after intravenous injections fall under one of the following heads:

1. Stimulation of the skin by a prick may cause death by reflex inhibition of the heart. I know the case of an infant in whom a pinprick of the toe to take blood for smear examination caused death.

2. Pricking the wall of a vessel by a needle may similarly cause death. In a case, as soon as the needle pierced the vessel wall for taking blood, death ensued.

3. Injections of large amounts of pyrogens. This is probably the cause of death after injections of dextrose.

4. Chemical stimulus to the vessel wall or the endocardium causing reflex inhibition of the heart. This is probably the case in mercurial diuretics, aminophylline, epinephrine and iodine solutions.

5. Anaphylactic shock. This is of the nature of histamine shock. The death after arsenicals is perhaps due to this.

A number of unavoidable factors contribute to intravenous fatalities. Young doctors who have to do intravenous administrations in hospital practice should not feel unnecessarily disturbed and guilty if a mishap occurs. They may thus be prevented from developing "speedphobia" and "speed neurosis" while doing their work.

P. L. Deshmukh, M.D.,
Hon. Physician,
Medical Dept, Sassoon Hospital,
Poona City, Indian Dominion.

DIAGNOSIS OF TUBERCULOSIS

To the Editor:—I hope you have space to publish a letter which appeared on July 30, 1948 in the *New York Times* and which was also sent to the National Tuberculosis Association. The author, Angela Koenig (Mrs. Robert P. Koenig) of Carmel, Ind., brings up a problem which is of the utmost importance for control and the ultimate eradication of tuberculosis. The means for diagnosing pulmonary tuberculosis are abundant. Unfortunately, a considerable portion of the practicing medical profession still fail to take advantage of them. Mrs. Koenig's letter furnishes a good illustration of such failure.

The Editor
The New York Times

Dear Sir,

Two months ago, five weeks after the birth of my second baby, I was found to be suffering from "moderately advanced" pulmonary tuberculosis. I should not consider this a matter of general interest did I not feel that my experience might serve as a warning and possibly save some other mother from a similar disaster. From what we have now learned about the disease it is apparent to my husband and me that I had been displaying obvious symptoms for some months. Yet, although I had a competent general practitioner as family doctor, was under the care of a good obstetrician and had visited an ear, nose and throat specialist, these symptoms were not correctly diagnosed. I complained to all three doctors of constant tiredness and a persistent cough. In fact, I spent some weeks in bed taking that modern cure-all, penicillin, for an infected sinus, which was judged to be the cause of my cough. It now appears that each doctor thought that one of the others would have taken up with me the possibility of tuberculosis, with the result that in the end none of them mentioned it to me or suggested that I should have an X-ray. Consequently, not only has my own life been endangered, but I have unknowingly exposed my babies to the appalling risks of miliary tuberculosis and tuberculous meningitis.

Since my illness I have heard of many cases of women breaking down with tuberculosis immediately after childbirth. My experience, and theirs, shows that, despite the magnificent work of the National Tuberculosis Association, much remains to be done. It is not only the general public which needs to be alerted to the dangers of tuberculosis, but the doctors themselves, and particularly the "specialists" in other branches of medicine, who tend to ignore the possibility of any illness outside their own field. In particular, I feel that the Tuberculosis Association should work to have the chest x-ray made as much a part of standard prenatal care as the blood test is now. And I would urge all prospective mothers to insist on an x-ray, for only thus can they be sure of safeguarding the health of themselves and their families at a time when they are apparently especially susceptible to the tubercle bacillus.

Yours very truly

Education of physicians who see cases of tuberculosis without recognizing them is still one of the most important responsibilities of medical teachers. Mrs. Koenig's letter is timely.

Esmond R. Long, M.D.,
Executive Secretary, American Trudeau Society.

Medical Economics

WHAT IS THE LEADING CAUSE OF DEATH?

Note.—*Summary of a monograph by Frank G. Dickinson, Ph.D., and Everett L. Welker, Ph.D., Director and Associate in Mathematics of the Bureau of Medical Economic Research of the American Medical Association. The monograph has just been published as Bureau Bulletin Number 64.*—Ed.

In view of the twenty-two year difference between the average ages at death from the leading "older" causes (heart, cancer, intracranial lesions of vascular origin and nephritis) and from the leading "younger" causes (accidents, pneumonia and influenza, and tuberculosis), the authors question the adequacy of numbers of deaths as the sole measure of the relative importance of the various causes. As an alternative to this traditional measure, they have developed two new measures for ranking the causes of death. These take into consideration the age at death as well as the number of deaths from each cause.

The authors call their two new measures "life years lost" and "working years lost." The number of life years lost from a given cause, say heart diseases, was obtained by multiplying the number of deaths at a given age from that cause by the life expectancy of a survivor of the same age and by then totaling the products for all ages. The unit of measure in this case is one "unrealized" year of life including the retired years as well as the productive years. The second new measure, "working years lost," is based on the working life expectancies of survivors of the same ages as the decedents. This technical term, "working life expectancy," is defined as the average number of years to be lived excluding those before the twentieth and after the sixty-fifth birthdays. The unit of measure here is one "unrealized" year of working life which includes only the working period, ages 20 to 65. Everyone below age 65 has a working life expectancy. The authors have taken a broad view of the potential economic productivity of all persons during the customary working period of life; thus their total of working years lost by death includes the "unrealized" years between ages 20 and 65 of all decedents, even housewives who are not generally classed as gainfully employed.

The authors have applied their two new measures to the seven leading causes of death in 1930, 1935, 1940 and 1945, using the voluminous data gathered and published by the National Office of Vital Statistics (Washington, D. C.). All causes other than the leading seven were grouped together under the caption "All Others," which accounted for 34 per cent of all deaths in 1930 and 26 per cent in 1945. The more complex actuarial concepts and computations involved in the two measures, and a breakdown by race and sex for 1945 only, are presented in two appendixes to the monograph.

During the fifteen year period covered by the study, the average age at death from all causes rose from 49 to 57 years—a testimonial to medical and social progress. Deaths from heart diseases increased from 19 per cent of all deaths in 1930 to 30

per cent in 1945, when "All Others" accounted for only 26 per cent. Deaths due to cancer rose from 9 to 13 per cent; accidental deaths accounted for about 7 per cent in each of the four quinquennial years. Despite the fact that heart diseases killed by far the largest number of persons each year, the authors contend that the evidence is inadequate to warrant the claim that heart diseases can be termed the leading cause of death for all purposes. They point out that the age at death is a necessary factor in gauging the loss to society resulting from the various causes. "Life years lost" and "working years lost" by death were developed as measures of this loss to society, not as measures of the infinite loss of the precious gift of life to the decedent or to the bereaved family. The Bureau hopes to make a second study using similar criteria to measure the loss to society from disability resulting from sicknesses and injuries, both fatal and nonfatal.

When applied to the leading causes of death in 1945, the two new measures produce surprising results. In that year deaths due to heart diseases destroyed 5,800,000 life years, cancer 2,900,000, accidents 2,800,000 and pneumonia 2,100,000. Deaths due to heart diseases were two and one-half times as numerous as deaths due to cancer, four and one-half times as numerous as accidental deaths and more than six times as numerous as deaths due to pneumonia. Despite the 4½ to 1 ratio, the number of life years lost from deaths due to heart diseases was only twice the number of life years lost by accidental deaths. The explanation lies in the average ages at death in 1945—age 68 for heart and age 46 for accidents. The corresponding average future lifetime were 11 and 26 years, respectively. Thus the 4½ to 1 lead of heart over accidents based on number of deaths was reduced to 2 to 1 when "life years lost" was the measure. The comparatively low average age at death from pneumonia in 1945 (46 years) accounted for a similar upgrading of that "younger" cause when ranked by "life years lost."

When the seven leading causes of death were ranked by "working years lost," accidents replaced heart in the number one position. In 1945, a year of nationwide gas rationing, the working years lost from accidental deaths numbered 1,750,000, while those from heart diseases numbered only 1,680,000. Pneumonia ranked third with 1,110,000 years and cancer fourth with 1,040,000 years. The breakdowns by race and sex presented in the appendix reveal that the young white male, who represents the productive and military strength of the country, was the special victim of accidents. In 1940 also, accidents were the number one destroyer of the customary working years of life; they ranked second in 1935 and third in 1930. Heart diseases were one rank below accidents in each of these four years, although the proportion of deaths from all causes which were due to heart diseases climbed from 19 to 30 per cent, while the proportion due to accidents remained at about 7 per cent. Evidently it has been a close race between these two leading causes when their relative importance is measured by working years lost, although pneumonia and tuberculosis outranked them in 1930 and pneumonia was first in 1935. Thus pneumonia has made way for accidents and heart diseases. Again the upgrading of the two "younger" causes is explained by the lower ages at death from these causes; the "unrealized" working years per death were far greater, on the average, for accidents and pneumonia than for heart and cancer. The authors note one statistic on medical progress which is of the utmost significance: in each of the four years studied, not one of the major fatal diseases of childhood was among the seven leaders.

The authors present their two new measures but do not state a preference for one over the other. They do contend that numbers of deaths in a period of declining mortality, longer life and a rapidly aging population cannot measure the loss to society from any one leading cause of death. If the retired, leisure years are a major consideration, then the authors recommend "life years lost" as the better of the two measures. If economic considerations are paramount, then the authors advise the use of their second new measure, "working years lost."

Although the natural causes of death—the physicians' problem—accounted for seven eighths and accidents for one eighth of the "working years lost" from deaths in 1945, the authors emphasize that the layman's role in prolonging life is greater than one eighth for he must be a cooperative patient and he must continue to support medical research and education if the accelerated rate of medical progress is to be maintained. As noted, the reason for the upgrading of fatal accidents by the second measure is the average age at death from the "older" causes. The fact that these "older" causes account for an increasing proportion of all deaths is an indication of medical progress. If this progress slows down and the average age at death eventually falls, accidental deaths would have to increase sharply in number or the average age at death from accidents would have to decline if that cause were to maintain first place as a destroyer of "unrealized" working years. Actually the average age at death from accidents has increased less since 1930 (4.5 years) than that from either of the other two "younger" causes, pneumonia and tuberculosis. As the authors point out, the real story here is medical progress and not an alarming increase in accidental deaths. In this sense, accidental deaths are a reflection of medical progress mirrored by the second new measure for ranking the leading causes of death.

Physicians not in close touch with mortality statistics will find parts of this monograph, replete with tables and charts, rather difficult yet thoroughly worth while. All physicians, particularly those who plan medical research and health improvement programs and the National Safety Council, other agencies engaged in the battle of accident prevention and public officials who must plan for our nation's health will do well to study the monograph carefully. The actuarial note on zero mortality assumptions in Appendix B will doubtless interest many workers in the field of vital statistics. Actually the answer to the question, "What is the leading cause of death?" is of vital interest to every man, woman and child in America.

All in all this study is a statistician's way of recording medical and social progress. So few die at the younger ages and ultimately die of the "older" causes that the remaining pieces of "unrealized" lifetimes have become very short. The pieces of "unrealized" working lifetimes are even shorter; in fact, they are so short in the case of deaths due to heart diseases in 1940 and 1945 that when these numerous short pieces are strung out end to end they do not stretch out as far as the fewer and longer pieces representing the "unrealized" productive years destroyed by accidental deaths. During recent decades these numerous short pieces have slowly lengthened as life expectancies above middle age have increased. The fact that these pieces have not lengthened more rapidly in recent years is rejected by the authors as proof of the charge that medical science has concentrated on the young to the neglect of the old; it is harder to add one additional year of future lifetime to the schedule of a 67 year old man than to the schedule of one who is only 45. The basic fact which motivated the Bureau's study and which accounts for the results presented in the monograph is that the population has aged, reflecting the cumulative results of medical progress of the past. One strongly suspects, however, that the typical American physician, thinking about his patients one by one, will continue to prize most highly that cure which will postpone the largest number of deaths among his patients.

Medical Motion Pictures

Bilateral Thyrotomy for Carcinoma of the Larynx. 16 mm., color, silent, 500 feet (1 reel), showing time fourteen minutes (sound speed). Prepared by Joseph I. Kemler, M.D., Baltimore. Produced in 1948 by Richard D. Grill, Department of Art, University of Maryland, Baltimore. Procurable on loan from the author, 1900 Eutaw Place, Baltimore 17.

The film shows the surgical technic of a new operation devised by the author for certain cases of carcinoma of the larynx. He states the operation is indicated in chordal tumors situated in the anterior two thirds of the larynx when there is no fixation of the cords. This is a presentation of a controversial new operative procedure but gives no claims as to end results or five year cures. It leans toward conservatism in a field in which the trend is toward more radical surgery. The surgical procedure is fairly well illustrated in color, but the film is titled in black and white stock, throwing either the titles or the operative procedure out of focus during projection. The use of black and white titles and drawings with color surgical photography is not good technic. Photography is good. This production is directed strictly to the specialist in laryngology and would not be of interest to a general medical audience.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Charitable Hospitals: Liability When Delirious Patient Jumps from Window.—The plaintiff sued for damages for the death of her husband, alleged to have been caused by the negligence of the defendant hospital. From a judgment for the plaintiff, the defendant appealed to the court of appeals of Tennessee.

According to the plaintiff's evidence, when her husband was admitted to the defendant hospital about 6 o'clock one evening he was extremely ill with pneumonia, his temperature was 106 F. and he was delirious. He was placed in a bed on the third floor about 3 feet from a window. His brother stayed with him until about 9:30 p. m., and was then told that visiting hours were over and that he must leave. He left under protest, but before leaving he told the nurses that someone should stay in the room or the patient, in his delirium, would try to get out of bed. One of the nurses said "I will tie him in bed if he tries to get up; I will keep him in bed some way." A few hours later, however, he got out of bed, climbed to the nearby window and fell to his death on a concrete porch below. The nurses testified that after the patient's brother left they put up sideboards, administered "sodium luminal" (phenobarbital sodium) and put the patient into restraints, consisting of straps tying his ankles and wrists to the bed.

In testing a hospital's liability for negligence, said the court, there is no distinction in this state between one operated for private gain and one conducted as a charity. In the instant case the defendant's nurses and interns knew that the plaintiff was suffering from pneumonia, had a very high temperature and was so irrational as to want to get out of bed and leave, yet they refused to let his brother stay with him and watch him or stay to see the doctor about getting a special nurse for him. They realized the patient was in danger from his delirium, said that they would tie him if he tried to get up and, by restraints, undertook to keep him from getting out of bed and harming himself, but they failed to fasten the restraints securely or at least to see that his restraints did not come loose. Despite the danger they failed to keep someone in his room to watch him, but left him in his delirium only a step from an unfastened and unguarded window. The admitted fact is, said the court, that the restraints did come loose, which could hardly have happened if they had been properly fastened and if the nurses had continually watched to keep them fastened. We think, the court continued, that the jury could have reasonably found, as it did, that the defendant failed to exercise ordinary care and diligence.

The defendant contended, however, that the patient's act of jumping out of the window was so unusual and extraordinary that it was altogether unforeseeable, that it was only a possibility and not a probability, and that the defendant cannot be charged with negligence for not foreseeing and guarding against such an act. The court said that the majority rule holds that if the defendant's conduct created an unreasonable risk of harm to the plaintiff the defendant is liable for all the injuries within the reasonable range of such risk, whether they could have been foreseen or not. The particular harm which actually befell the patient need not have been foreseeable; it is enough that some such harm of a like general character was reasonably foreseeable as a likely result of defendant's failure to use due care to keep him in bed and to protect him against getting out of the window in his delirium. We think, the court concluded, that the jury could well have found that the patient's act was not so unusual or extraordinary as to be beyond range or reasonable expectation but that it was a thing which might reasonably have been expected to occur in view of his condition. Common experience shows that patients in such condition often jump or fall out of upper story windows of hospitals.

Finally the defendant contended that there was no evidence to show that the patient might not have died of pneumonia even if he had had no accident. There is no merit in such a contention, said the court. There was ample evidence to support the jury's finding that the patient's death was caused by the injuries he sustained in the accident. The fact that he was ill, even if it could be said he might later have died of such illness, did not prevent the defendant's negligence from being the legal or proximate cause of his death. Accordingly the judgment in favor of the plaintiff was affirmed and the hospital was held liable in damages for the patient's death.—*Spivey v. St. Thomas Hospital, 211 S. W. (2d) 450 (Tenn., 1948).*

Evidence: Physician's Qualifications to Testify Concerning Roentgenograms.—The defendant was charged with murder and convicted of manslaughter, from which conviction he appealed to the Supreme Court of Mississippi.

During the trial of the case the court admitted in evidence roentgenograms showing the course of the bullet through, and the place of its lodgment in, the head of the deceased. The defendant contended that this was reversible error because it was not shown, with sufficient certainty, that the roentgenograms were accurately made or that Dr. Butler, who explained them to the jury, had the required skill and knowledge to interpret them.

The victim was taken to the McComb City Hospital, McComb, Miss., immediately after being shot in the head with a pistol by the defendant. He lived only a short time and after his death the roentgenograms in question were taken. They were made, with the machine and instruments used in the hospital for that purpose by Dr. Moore, assisted by Dr. Butler, both professionally connected with the hospital, and were preserved as a record of the hospital. Dr. Butler graduated from the University of Tennessee Medical College in 1939 and later served an internship at Grace Hospital, Detroit. He then practiced medicine in the Marine Corps for three and a half years and had engaged in the general practice of medicine since 1941. He testified that he had never taken a technical course of study directed particularly to making or reading roentgenograms, but he had studied both subjects as a part of his medical course and his practical experience therein, both as a student and in the practice of medicine, had been extensive. He also testified that the roentgenograms in question were accurately taken and interpreted and there was no evidence to the contrary.

The Supreme Court said that the process of roentgenography is now well established as a method of securing a reliable representation of the bones of the human body and the location of growths and foreign substances in the body. They are admissible on authentication which satisfies the court that the thing or person is fairly portrayed, and the question of the competency of roentgenograms is a preliminary one addressed to the sound discretion of the court. We cannot say, the Supreme Court concluded, that the trial court erred in admitting these roentgenograms in evidence.

The question of the qualifications of Dr. Butler to interpret the roentgenograms is also one normally addressed to the sound discretion of the trial court. Any person who has by sufficient experience acquired adequate knowledge of roentgenograms and their interpretation may qualify as a witness. It is a general rule that for one to testify as an expert it is not necessary that he be infallible or possess the highest degree of skill. It is sufficient if he possesses peculiar knowledge, wisdom or information regarding the subject matter, acquired by study, investigation, observation, experience or practice, not possessed by the ordinary layman or inexperienced person. It is evident, we think, from the foregoing evidence that Dr. Butler was well qualified to interpret these roentgenograms.

The Supreme Court accordingly held that the physician had been properly qualified as an expert and that the roentgenograms had been accurately taken and interpreted. The judgment of conviction was affirmed. *Wallace v. State, 35 So. (2d) 703 (Miss., 1948).*

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1937 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Heart Journal, St. Louis

35:873-1058 (June) 1948

Effect of Ergot Derivatives on Circulation in Man with Special Reference to Two New Hydrogenated Compounds (Dihydroergotamine and Dihydroergocornine). H. J. Bluntschli and R. H. Goetz.—p. 873.
Terminal Electrocardiographic Patterns in Experimental Anemia, Coronary Occlusion, and Hemorrhagic Shock. A. S. Harris.—p. 895.
*Terminal Electrocardiograms: Twenty-Three Case Reports and Review of Literature. M. W. Stroud and H. S. Feil.—p. 910.
Changing Intensity of First Sound in Auricular Flutter, Aid to Diagnosis by Auscultation. W. P. Harvey and S. A. Levine.—p. 924.
*Oxygenation Studies in Congenital Pulmonary Stenosis: Application of Recording Oximetry in Evaluation of Cardiorespiratory Function. G. Gullickson, J. O. Elam, Margaret Hammond and others.—p. 940.
Wolff-Parkinson-White Syndrome with Myocardial Infarction: Experimental Study. Irene G. Tamagna, J. S. Butterworth and C. A. Poindexter.—p. 948.
Cardiac Vibrational Intensity and Cardiac Output. J. H. Foulger, P. E. Smith Jr. and A. J. Fleming.—p. 953.
Respiratory Movement as Factor in Production of Q Waves in Lead I and in Unipolar Leads from Left Precordium in Human Left Bundle Branch Block. A. W. Lapin and H. B. Sprague.—p. 962.
Electrokymographic Studies of Asynchronism of Ejection from Ventricles: Normal Subjects and Patients with Bundle Branch Block. G. F. Ellinger, F. G. Gillich, B. R. Boone and W. E. Chamberlain.—p. 971.
Evidence for Generalized Arteriolar Constriction in Coarctation of Aorta. E. Hull.—p. 980.
Observations Concerning Influence of Calcium on Actions of Digitalis Glycoside. M. Friedman and R. Bine Jr.—p. 984.
Nomogram for Rate Correction of Q-T Interval in Electrocardiogram. M. Kissin, M. M. Schwarzschild and H. Bakst.—p. 990.

Terminal Electrocardiogram.—Stroud and Feil present 23 cases in which electrocardiograms were obtained before and during the terminal activity of the heart. The electrodes were attached to the moribund patient before clinical death. The three standard leads were obtained and also a few chest leads. Tracings were taken intermittently or continuously on lead II until the string became motionless. Several electrocardiograms were obtained during operations with patients under general anesthesia. The 23 patients ranged in age from 10 to 87 years. No definite heart disease could be found in 7 cases. In 1 of the latter sudden death was due to ventricular fibrillation, while in 3, ventricular fibrillation was but the terminal phase, occurring long after "clinical" death. The remaining 3 patients of this group showed no ventricular fibrillation. The heart slowed and then stopped abruptly. Of the 16 cases of obvious heart disease, 7 ended with ventricular fibrillation. Of the 8 patients with recent or old myocardial infarction, 4 died suddenly as a result of the abrupt onset of ventricular fibrillation, while the other 4 patients died suddenly with slowing and abrupt standstill. Fifteen of the 16 patients with diseased hearts died rapidly. In only 5 of these was death directly due to the onset of ventricular fibrillation.

Oxygenation Studies in Congenital Pulmonary Stenosis.—Gullickson and his associates say that the Blalock-Taussig operation has been performed in 14 instances of the tetralogy of Fallot at the University of Minnesota Hospitals. Physiologic studies of pulmonary oxygenation were made in 10 of these patients by means of recording oximetry, and of these 2 representative cases are presented. The studies were carried out preoperatively, during the operation and postoperatively. Two important facts were revealed. First, the rise in arterial oxygen saturation on the establishment of the systemic-pulmonary arterial shunt was practically immediate, and, second, the saturation time on administration of 100 per cent oxygen was greatly shortened after the operation. The first observation indicated that the shunt had a direct primary beneficial effect on arterial oxygen saturation. The second would seem to show that the net effect of the operation was to increase the fraction of the total cardiac output supplying the pulmonary vascular bed. The implication from these observations is that the shunt resulted in a substantial improvement in the functional capacity of aeration of blood.

American Journal of Surgery, New York

76:757-866 (June) 1948. Partial Index

Posterior Sphincterotomy. E. T. Whitney.—p. 761.
Clinical Studies of Liver Function: Hepatorenal Syndrome. C. R. Schmidt and V. E. Chesky.—p. 772.
Double Fractures and Double Non-Unions of Shaft of Tibia. H. May.—p. 796.
Extraperitoneal Cesarean Section as Procedure of Choice. R. A. Cacciarelli.—p. 802.
Modern Management of Megacolon. B. M. Bosworth, H. D. Stein and J. R. Lisa.—p. 808.
Various Anesthetics in Orthopedic Surgery. B. B. Sankey and L. E. Campbell.—p. 817.
The Critically Burned Child. J. C. Urkov.—p. 821.
Richter's Hernia. D. Lyall and R. Luomanen.—p. 828.

American Journal of Tropical Medicine, Baltimore

28:349-514 (May) 1948. Partial Index

Food and Malaria. E. I. Salisbury.—p. 349.
Shigellae Occurring in Japan. W. L. Barksdale.—p. 359.
Pneumonic Plague: Report of Recovery in Proved Case and Note on Sulfadiazine Prophylaxis. C. H. Huang, C. Y. Huang, L. W. Chu and T. F. Huang.—p. 361.
Incidence and Control of Amebiasis and Other Intestinal Protozoan Infections in Memphis Hospital. H. H. Anderson, H. G. Johnstone, H. Pacher and others.—p. 373.
Quinacrine Levels in Plasma of Persons with Infectious Jaundice During and After Suppressive Malaria Therapy. J. Maier.—p. 395.
Absorption of Quinine and Quinacrine in Dysentery Patients. J. Maier.—p. 397.
Comparison of Effectiveness of Quinacrine and Quinine Against Falciparum Malaria. J. Maier, F. B. Bang and N. G. Hairston.—p. 401.
Field Trial of Chloroquine (SN 7618) as Suppressive Against Malaria in Philippines. J. Maier.—p. 407.
Study of Prophylactic, Curative and Suppressive Activity of SN-11,437 (Metachloridine) in Standardized Infections of Vivax Malaria. T. N. Pullman, A. S. Alving, R. Jones Jr. and others.—p. 413.
Intercurrent Infections of Carrion's Disease Observed in Peru. W. E. Ricketts.—p. 437.
*Rabies, The Physician's Dilemma. T. F. Sellers.—p. 453.
Yellow Fever Reservoir of Orinoco-Amazon Basin. J. Boshell-Manrique.—p. 457.
Studies on Transmission of Filarial Worms of Cotton Rat. J. A. Scott.—p. 481.
Rearing and Maintaining Laboratory Colony of Body Lice on Rabbits. G. H. Culpepper.—p. 499.

Rabies, the Physician's Dilemma.—After thirty years of practical experience, it is Sellers' belief that antirabic vaccine is not harmless and that it has caused more deaths than has rabies when given to persons only indirectly or remotely exposed. Since 1925, the Georgia Department of Public Health has furnished treatment for more than 50,000 persons, in 7 of whom treatment paralysis developed. Whereas in the material reviewed by the author the incidence of paralytic accidents was 1 in every 7,200 persons treated, other authors have reported an incidence of 1 in 3,000 cases. Of the 7 cases of treatment paralysis encountered in Georgia, 4 terminated fatally. Only 2 occurred in persons treated because they were actually bitten by rabid dogs. Five were in persons only remotely exposed, treated mainly to allay undue apprehension. Of these 5, 3 died. Five were in persons who had previously received antirabic vaccine. A study of 32 post-treatment fatalities due to rabies occurring among 50,000 persons treated in Georgia since 1925 reveals that 19, or 60 per cent, of these deaths occurred in persons bitten severely on the face. In no instance did rabies develop after superficial face wounds. The death rate per thousand treated for face bites was 7.9 per cent. The death rate per thousand treated for hand and arm bites was 0.5 per cent. Only 1 death followed bites on the lower extremities, a rate of 0.1 per thousand treated. Bites on the body also had a death rate of 0.1 per thousand treated. The author cites conditions under which antirabic treatment is advisable or contraindicated. He is convinced that it is not hydrophobia but rather rabiphobia which constitutes the major and most troublesome problem to the practicing physician and health officer. The administration of antirabic vaccine to persons actually bitten or scratched by the teeth of known or suspectedly rabid animals is a relatively

simple and justifiable procedure regardless of the outcome, in that the danger of the disease is far greater and more serious than any ill effects from the vaccine, but for exposures other than actual bites, the danger of treatment complications far exceeds that of either rabies or rabiphobia.

American Practitioner, Philadelphia

2:635-702 (June) 1948. Partial Index

Physiologic Therapy of Intractable Bronchial Asthma and Status Asthmaticus. A. L. Barach.—p. 635.
Anthallan Therapy in Infantile Eczema. M. S. Kleckner Jr.—p. 639.
Newer Antihistaminic Drugs in Symptomatic Treatment of Allergic Manifestations. S. Friedlaender and A. S. Friedlaender.—p. 643.
Recent Hazards in Treatment of Appendicitis. E. Holman.—p. 648.
*Prevention of Turnover in Hospital Personnel: Incentives. M. H. Eichentaub.—p. 655.
Standard Method for Reporting Blood Sedimentation Tests. L. M. Hershenson and M. A. Hershenson.—p. 661.
Simple Approach to Study of Vaginal Smears: I. Variations in Normal Sexual Cycle. R. G. Bonime.—p. 664.
Recognition of Incipient Hyperthyroidism. R. E. Swenson and G. M. Curtis.—p. 671.
Physiology of Adrenals as Related to Addison's Disease, Virilism and Cushing's Syndrome. J. E. Howard.—p. 674.
Peritonitis, Simulating Tuberculous Peritonitis, Due to Rupture of Dermoid Cyst of Ovary. S. G. Odle and S. A. Rosenburg.—p. 686.

Prevention of Turnover in Hospital Personnel.—Eichentaub deplores the lack of adequate employment incentives in most hospitals and believes that this is causing excessive turnover. The hospital employee has had no economic security when sickness and old age have deprived him or her of the ability to work. Long hours of work and insufficient vacations are other outstanding causes of rapid turnover of personnel in the hospital. At the outset the employee should be shown a progress chart and told that he will be rated for such performances as quality of work, quantity of work, knowledge of job, dependability, initiative, cooperation, personality, ability to learn, attendance and judgment. At the end of ten days' employment, the personnel director should hold an interview to determine whether the employee likes the work, is becoming adjusted, gets along with the supervisor, is thoroughly familiar with the rules and regulations or feels overworked. This ten day follow-up interview is a crucial period. The next interview should be at the end of thirty days. It is important that every employee be interviewed before leaving the organization. Many leave because of some petty irritation or annoyance that can be "talked out." An important factor is recognition of the employee's work. This is one of the most powerful human incentives.

American Review of Tuberculosis, New York

57:433-546 (May) 1948

*Pneumoperitoneum in Treatment of Pulmonary Tuberculosis: 407 Consecutive Cases. H. G. Trimble, J. L. Eaton, G. L. Crenshaw and Ina Gourley.—p. 433.
Extrapleural Pneumothorax. J. R. Head and C. W. Moen.—p. 471.
Bed-Rest in Thrombo-Embolization in Tuberculosis. T. T. Fox, E. H. Robitzek, I. Bernstein and Audrie L. Bobb.—p. 485.
Treatment with Antireticular Cytotoxic Serum in Pulmonary Tuberculosis. H. R. Nayer.—p. 489.
Pleural Fat Pads: Cause of Thoracic Shadows. L. C. Evander.—p. 495.
Effect of Benadryl Hydrochloride on Tuberculin Reaction in Guinea Pigs. R. W. Sarber.—p. 504.
Medical Aspects of Rehabilitation. Study on 175 Veterans with Arrested Pulmonary Tuberculosis. I. Pine.—p. 511.
Role of Family in Control of Tuberculosis. H. Hudson.—p. 519.

Pneumoperitoneum in Pulmonary Tuberculosis.—Trimble and his co-workers treated 407 patients with pulmonary tuberculosis by pneumoperitoneum. Three hundred and eighty-two of these, 160 men and 222 women, more than half of whom were between the ages of 21 and 40 and one fifth of whom were over 51, were analyzed according to results. In 218 patients (57 per cent) the disease became arrested, and an additional 48 (13 per cent) were definitely improved with cavity closed and three day sputum negative to concentration at weekly intervals for two months. The number of complications severe enough so that pneumoperitoneum was discontinued varied from 23 to 28, depending on the point of view. Analysis according to the extent of pulmonary disease showed that arrest occurred in 28 of the 34 patients with minimal pulmonary tuberculosis; in 107 of the 135 with moderately advanced, and in 83 of the 213 with far advanced tuberculosis. In 106 of the 223 patients with cavitation, the disease became arrested, and another 40 were definitely improved. The position of the cavity within the lung, whether apical, in the midlung field or basal, made no statistically significant difference in the results obtained. In the 135 patients with moderately advanced disease, no marked difference was apparent between those with and those without cavitation; in 33 of the 45 with cavitation the disease became arrested, and in 74 of the 90 without cavitation; in the 213 cases of far advanced disease a decided difference was shown in favor of those with cavitation; in 73 of the 178 with cavitation the disease became arrested, in comparison with 10 of the 35 without cavitation. Results of pneumoperitoneum therapy in pulmonary tuberculosis complicated by pleurisy with effusion were gratifying, but were in general unsatisfactory in silicotuberculosis and not good in pulmonary tuberculosis complicated by tuberculous tracheobronchitis when compared with cases with cavity.

Archives of Physical Medicine, Chicago

29:327-380 (June) 1948

Neurophysical Aspects of Therapy in Cerebral Palsy. T. Fay.—p. 327.
Hypothesis to Explain Muscular After Effects of Poliomyelitis. M. E. Knapp.—p. 334.
Corrective Physical Rehabilitation for Neuropsychiatric Patients. J. E. Davis.—p. 345.
*Use of Tetanizing Current in Myasthenia Gravis: Report of Case. J. L. Rudd and J. F. Cullinan.—p. 354.
Evaluation of Hemoirradiation Therapy. F. B. Moor, R. E. Hoyt and M. G. Levine.—p. 358.

Tetanizing Current in Myasthenia Gravis.—Rudd and Cullinan believe that involved muscles in a patient with myasthenia gravis could be kept in normal tone if exercised judiciously. They report the case of a man, aged 53, who had ptosis of the right eyelid and who was supporting his mandible because of weakness of the masseter muscle. An attempt was made to increase the strength of the muscles and prevent progressive atrophy of disuse. The masseters were selected for treatment with a tetanizing current. Test results were used as a guide to determine the number of contractions to be eliminated during treatment. Improvement was noted within a week. In the fatigue tests, a greater number of contractions were produced without reaching the absolute fatigue point. After the patient had received the second treatment, ten contractions were elicited from the left masseter. Five days later in a fatigue test the number was 120. The number of contractions produced at treatment sessions between the aforementioned dates was seven. Two weeks later a fatigue test showed that the originally weaker right masseter had caught up with the left one, with 200 contractions elicited. After this test, sixty treatment contractions were given to each masseter. The paticnt lost the numbness on the right side of the face which had been present since the onset of the disease. A drooling from the side of the mouth, a source of considerable annoyance to the patient, had ceased. On palpitation the masseters appeared to be of normal tone. The patient stated "My face seems to be alive again." The final fatigue test was carried out on the forty-seventh day. Four hundred contractions were elicited from each masseter, an increase of approximately 400 per cent in forty-seven days. It was felt that the objective of increasing the strength of the masseter muscles had been reached.

Bulletin New York Academy of Medicine, New York

24:341-408 (June) 1948. Partial Index

Testicular Dysfunction. E. P. McCullagh.—p. 341.
Effect of Immobilization on Metabolic and Physiological Functions of Normal Men. J. E. Deitrick.—p. 364.
Clinical Significance of Nutritional Deficiencies in Pregnancy. W. T. Tompkins.—p. 376.
Changed Status of Diphtheria Immunity. P. Cohen, H. Schneck, E. Dubow and S. Q. Cohlan.—p. 389.
Changes in Lysozyme Formation in Human Colon in Various Emotional States. W. J. Grace, P. H. Seton, S. Wolf and H. G. Wolff.—p. 390.
*Use of Para-Aminobenzoic Acid in Amebiasis: Preliminary Report. K. G. Dwork.—p. 391.
Differential Diagnosis of Diaphragmatic Hernia and Coronary Heart Disease. S. Dack, J. Stone, A. Grishman and A. M. Master.—p. 396.
*Aspiration of Bone Marrow from Iliac Crest: Technical and Diagnostic Advantages versus Sternal Aspiration. M. A. Rubinstein.—p. 400.

Para-Aminobenzoic Acid in Amebiasis.—Dwork treated 12 patients with amebiasis with sodium salt of para-aminobenzoic acid, purely on an empiric basis. It was possible to evaluate the results of treatment in 9 of the 12 cases. Evidence of clinical

and laboratory arrest of the disease followed administration of sodium para-aminobenzoic acid in 4 of the 9 cases. Of the 7 patients with symptoms, all but 1 showed disappearance of or improvement in symptoms following treatment.

Aspiration of Bone Marrow from Iliac Crest.—Rubinstein shows that the aspiration of bone marrow from the iliac crest has the advantage that no serious injury can be sustained by any underlying organ. The procedure is less painful, and the patient is less apprehensive than when subjected to a puncture in the cardiac area. Puncture of the iliac crest can easily be performed at frequent intervals at both sides of the body, and is therefore suitable for serial bone marrow studies. Bone marrow cavities of the iliac crest can occasionally be used as a route of administering fluids into the general circulation. The cells of the iliac bone marrow have been studied for the past four and a half years in about 1,000 different cases showing normal and pathologic findings. In about 300 of these instances, simultaneous sternal marrow studies were also performed. In certain instances the iliac aspiration has proved of distinct diagnostic advantage, as compared with the sternal aspiration alone.

Bull. of U. S. Army Med. Dept., Washington, D. C.

8:411-492 (June) 1948

What Every Medical Officer Should Know About the Atomic Bomb. Office of The Surgeon General.—p. 422.
Psychosurgery. W. Freeman and J. W. Watts.—p. 434.
Acute Appendicitis. R. N. Schullinger.—p. 436.
Determinations of p_H of Pacific Oysters. W. J. Carr, R. B. Anderson and C. W. Betrold.—p. 442.
Treatment of Surgical Infections with Antibiotics. F. Meleney.—p. 445.
Fractures and Dislocations of Spine. J. C. McCauley Jr.—p. 451.
Infectious Arthritides. J. J. Bunim.—p. 458.
Diabetes Mellitus. M. Handelsman.—p. 463.
Management of Venereal Disease Cases in First Army Area. G. J. Carroll.—p. 469.
Estimation of Streptomycin Sensitivity of Bacteria. A. Ehrlich.—p. 473.
Estimation of Streptomycin in Blood Serum. A. Ehrlich.—p. 476.
Infarction of Auricle. I. Graef.—p. 481.
Surgical Management of Regional Ileocolitis. F. Glenn.—p. 485.
Modern Concept of Pulmonary Tuberculosis. G. G. Ornstein.—p. 489.

Georgia Medical Association Journal, Atlanta

37:167-202 (May) 1948

Current Problems of Organized Medicine. S. P. Kenyon.—p. 167.
Bismuth Therapy for Colds. T. Levy.—p. 172.
Early Ambulation and Related Aspects of Postoperative Surgical Management. C. S. Pittman Jr.—p. 174.
Xanthomatous Tumors of Achilles Tendon. H. B. Jenkins.—p. 176.
Amebic Abscess of Liver. J. D. Martin Jr.—p. 178.
Chronic Lymphatic Leukemia Occurring Simultaneously in Brothers. H. C. Freeh.—p. 183.
Physician and Public Relations. G. Middlebrooks.—p. 184.

Journal of Clin. Endocrinology, Springfield, Ill.

8:345-422 (May) 1948

Classification of Male Hypogonadism and Discussion of Pathologic Physiology, Diagnosis and Treatment. C. T. Heller and W. O. Nelson.—p. 345.
Male Pseudohermaphroditism Proved by Surgical Exploration and Microscopic Examination: Case Report with Speculations Concerning Pathogenesis. M. B. Goldberg and A. F. Maxwell.—p. 367.
*Relation Between Infant Birthweight and Subsequent Development of Maternal Diabetes Mellitus. J. P. Kriss and P. H. Futcher.—p. 380.
Extreme Leydig Cell Hyperplasia Associated with 2 Other Endocrine Changes: Case Report. E. L. Wilbur and R. A. Burger.—p. 390.
Necropsy Study of Case of Turner's Syndrome. A. Atria, R. Sans and S. Donoso.—p. 397.
Induction of Uterine Bleeding in Amenorrhea with Single Injection of Precipitates of Estrone and Progesterone. B. Zondek and S. Rozin.—p. 406.

Infant Birthweight and Subsequent Development of Diabetes Mellitus.—Diabetic women frequently give birth to unusually large infants. Infants of excessive weight may be born to mothers before clinically apparent maternal diabetes mellitus develops. Kriss and Futcher attempted to ascertain how the birthweight of an unusually large baby can be correlated with the likelihood of subsequent development of maternal diabetes. They analyzed the birthweight data on infants born to 100 women in whom diabetes mellitus later developed and on infants born to two control groups. They found that the birth of an infant weighing over 10 pounds (4,536 Gm.) may herald the development of diabetes in the mother. The average birthweight of infants born to prediabetic mothers is greater than that of infants born to normal mothers. The period between the birth of the first abnormally large infant and the development of clinical diabetes in the mother averaged about twenty-four years, with a range of one to forty-six years. The authors have constructed a table permitting rough estimation of the accuracy with which one may predict the subsequent development of diabetes in a woman giving birth to a baby weighing in excess of ten pounds. The table shows that as the birthweight of the baby rises, the prediction accuracy increases progressively and is greater than 60 per cent when the baby weighs more than 13 pounds.

Journal of Experimental Medicine, New York

87:369-456 (May) 1948

Antibody Response in Rabbits to Killed Suspensions of Pathogenic T. Pallidum. H. Eagle and R. Fleischman.—p. 369.
Inhibitory Effect of Polysaccharide on Mumps Virus Multiplication. H. S. Ginsberg, W. F. Goebel and F. L. Horsfall Jr.—p. 385.
Effect of Polysaccharides on Reaction Between Erythrocytes and Viruses, with Particular Reference to Mumps Virus. H. S. Ginsberg, W. F. Goebel and F. L. Horsfall Jr.—p. 411.
Osmotic System Within the Cytoplasm of Cells. E. L. Opie.—p. 425.
Inactivation of Biologically Active Proteins, and Virus of Western Equine Encephalomyelitis by Periodic Acid. W. F. Goebel, P. K. Olitsky and A. C. Saenz.—p. 445.

87:457-606 (June) 1948. Partial Index

Protein Metabolism and Exchange as Influenced by Constriction of Vena Cava. Experimental Ascites an Internal Plasmapheresis: Sodium Chloride and Protein Intake Predominant Factors. F. W. McKee, P. R. Schkuerb, J. A. Schilling and others.—p. 457.
Determination of Concentration of Dye T-1824 in Normal and Lipemic Plasmas. F. P. Chinard and H. A. Eder.—p. 473.
Effect of Nitrogen Mustards on Enzymes and Tissue Metabolism. E. S. G. Barron, G. R. Bartlett and Zelma Baker Miller.—p. 489.
Variation Occurring in Group A Streptococci During Human Infection. Progressive Loss of M Substance Correlated with Increasing Susceptibility to Bacteriostasis. S. Rothbard and R. T. Watson.—p. 521.
Reversibility of O-D Type of Influenza Virus Variation. T. P. Magill and J. Y. Sugg.—p. 535.
Parenteral Plasma Protein Maintains Nitrogen Equilibrium Over Long Periods. R. Terry, W. E. Sandrock, R. E. Nye Jr. and G. H. Whipple.—p. 547.

Journal of Infectious Diseases, Chicago

82:197-308 (May-June) 1948

Use of Mice in Experimental Chemotherapy of Tuberculosis. G. W. Raleigh and G. P. Youmans.—p. 197.
Effect of Arsenicals and Antimonials on Activity of Glycolytic Enzymes in Lysed Preparation of Trypanosoma Equiperdum. G. Chen.—p. 226.
Studies on Immunity to Asiatic Cholera: V. Absorption of Immune Globulin from Bowel and Its Excretion in Urine and Feces of Experimental Animals and Human Volunteers. W. Burrows and I. Havens.—p. 231.
Effect of Artificial Blood Meals Containing Hydroxynaphthoquinone M2279 on Developmental Cycle of Plasmodium Gallinaceum in Aedes Aegypti. L. Whitman.—p. 251.
Studies on Leptospira Icterohaemorrhagiae: IV. Survival in Water and Sewage: Destruction in Water by Halogen Compounds, Synthetic Detergents, and Heat. S. L. Chang, M. Buckingham and M. P. Taylor.—p. 256.
Components of Tubercle Bacillus Responsible for Delayed Type of "Infectious" Allergy. S. Raffel.—p. 267.
*Laboratory Study of Epidemiology of Poliomyelitis. F. B. Gordon, F. M. Schabel Jr., A. E. Casey and W. I. Fishbein.—p. 294.
Respiratory Pathogenicity of Brucella. S. S. Elberg and S. W. Henderson.—p. 302.

Epidemiology of Poliomyelitis.—Gordon and his associates say that in 1945 an epidemiologic study of poliomyelitis was organized in Chicago under the auspices of the Chicago Health Department. The method was to make a survey of the neighborhoods of verified cases of paralysis during which a certain number of contacts and noncontacts were selected for intensive study. Some results had been reported previously. Pools of daily stool collections from 76 persons were tested by inoculation of 2 monkeys each. Of 23 household contacts, 17 were infected as evidenced by virus in the stool. The incidence of infection in extra-household contacts was 9 of 23, and in noncontacts living in the same neighborhood, 2 of 18. None of 5 persons from nonpoliomyelitis (control) neighborhoods and 1 of 7 unclassified persons were infected. These results are interpreted as indicating that during this epidemic period contact with an infected person was the usual source of infection within the groups studied rather than any general widespread factor in the neighborhood.

Journal of Lab. and Clinical Medicine, St. Louis

33:521-650 (May) 1948. Partial Index

*Penicillin in Treatment of Actinomycosis. D. R. Nichols and W. F. Herrell.—p. 521.
Maternal Isoimmunization Without Evidence of Clinical Erythroblastosis Fetalis in Newborn. W. L. Donohue and I. A. Fremes.—p. 526.
Anemia of Infection: IX. Influence of Adrenalectomy and of Adrenal Cortical Hormone on Hypoferremia and Other Blood Changes Associated with Injection of Turpentine. D. N. Majumder and M. M. Wintrobe.—p. 532.
*Idiopathic (Familial) Hypoprothrombinemia. P. S. Hagen and C. J. Watson.—p. 542.
Observations on Alcoholic Fatty Liver: Use of Interval Needle Biopsy and Liver Function Tests. R. E. Buck.—p. 555.
Ethylene Glycol Poisoning: Clinical and Pathologic Study of 3 Cases. P. O. Hagemann and T. R. Chiffelle.—p. 573.
Action of Pilocarpine on Lungs in Normal and Asthmatic Subjects. J. J. Curry and S. E. Leard.—p. 585.
Variations in Dermal Absorption with Age. J. Strauss Jr. and H. Necheles.—p. 612.
Electrophoretic Study of Blood Serum from Lymphogranulomatous Patients. A. Rottino, Diana Suchoff and K. G. Stern.—p. 624.

Penicillin in Actinomycosis.—Nichols and Herrell report on 46 patients with actinomycosis treated with penicillin and followed up for one to five years. Of 26 patients with cervicofacial actinomycosis, 24 had excellent results. These results were obtained after an average period of treatment of less than two months, a period significantly less than that required to obtain comparable results when penicillin was not used. Of 9 patients with pulmonary actinomycosis, 5 recovered, and of 8 patients with abdominal actinomycosis, 6 recovered. All 3 patients with pelvic actinomycosis recovered. All strains of Actinomyces bovis cultured from these patients were sensitive to penicillin in vitro. Penicillin appears to be an effective chemotherapeutic agent in the treatment of actinomycosis and a useful adjunct to other forms of therapy.

Idiopathic, Familial, Hypoprothrombinemia.—Hagen and Watson point out that an instance of idiopathic hypoprothrombinemia as the basis of a hemorrhagic diathesis was first reported in 1941 and that since then 8 additional cases have been reported. Familial hypoprothrombinemia has been demonstrated in at least 4 instances. Most of the patients thus far reported were not followed in detail over a long period of years, but the patient whose case is analyzed in this report was seen repeatedly since December 1937, when she was 20 years old. She was admitted for study and treatment of an eight year bleeding tendency. A variety of studies and therapeutic attempts were made over a ten year period in order to ascertain the exact pathologic mechanism. All the known factors other than hypoprothrombinemia which might give rise to a delay in prothrombin time were presumably excluded by the experiments. There was an evident lack of the prothrombin factor which is decreased by "dicumarol." There was no response to vitamin K, while plasma of various ages was consistently effective. The regular occurrence of a positive cephalin flocculation reaction, together with the presence of a cryoglobulin in the patient's serum, tends to support the concept of a primary disturbance of protein synthesis in the liver. The most important result of the studies was the evidence of familial incidence of the disorder. This is the fifth reported instance of familial hypoprothrombinemia.

Journal of Neurophysiology, Springfield, Ill.

11:153-276 (May) 1948. Partial Index

Electroencephalogram (EEG) in Curarized Mammals. E. Girden.—p. 169.
Corticocortical Connections of Superior Surface of Temporal Operculum in Monkey (Macaca Mulatta). O. Sugar, J. D. French and J. G. Chusid.—p. 175.
Babinski Sign Extinction During Bilateral Simultaneous Cutaneous Stimulation. R. Cohn.—p. 193.
Afferent Fibers in Muscle Nerves. D. P. C. Lloyd and Hsiang-Tung Chang.—p. 199.
Double Discharges in Human Motor Units. J. S. Denslow.—209.
Extension of "Law of Denervation" to Afferent Neurones. C. G. Drake and G. W. Stavraky.—p. 229.
Neural Organization of Retinal Elements, as Revealed by Polarization. R. Granit.—p. 239.
Differential Action of Anoxia, Asphyxia and Carbon Dioxide on Normal and Convulsive Potentials. E. Gellhorn and C. Heymans.—p. 261.

Journal of Pediatrics, St. Louis

33:479-628 (May) 1948

Radiographic Appearance of Gastrointestinal Tract During the First Day of Life. M. G. Wasch and A. Marck.—p. 479.
*Use of Benzedrine and Dexedrine Sulfate in Treatment of Epilepsy. S. Livingston, L. Kajdi and E. M. Bridge.—p. 490.
Diagnosis and Surgical Treatment of Certain Congenital Cardiovascular Anomalies. M. J. Carson and T. H. Burford.—p. 495.
*Evaluation of Penicillin Treatment in Early Congenital Syphilis. L. P. Barker.—p. 516.
New Concepts of Osteomyelitis in Newborn Infant. C. G. Hutter Jr. —p. 522.
Relationship of Race to Incidence of Diphtheria and to Schick, Tuberculin, and Wassermann Tests in Hospitalized Children.—p. 530.
Varicelliform Eruption of Kaposi Due to Vaccinia Virus Complicating Atopic Eczema. J. H. Fries, S. Borne and H. L. Barnes.—p. 532.
Proctologic Examination of Infants and Children. S. Schapiro.—p. 543.
Some of Problems in Education of Rheumatic Children. J. Levitt and L. M. Taran.—p. 553.

Amphetamine and Dextro-Amphetamine Sulfate for Epilepsy.—Livingston and his associates report on 85 patients of the Epilepsy Clinic of the Johns Hopkins Hospital treated with amphetamine sulfate or its dextrorotatory component, dextro-amphetamine sulfate. Approximately one half of these patients did not respond to the usual forms of therapy, not including trimethadione, which was not available at the time of this study. The remainder of the patients had received no other forms of medication. Fifty-one patients had idiopathic epilepsy and 34 had organic epilepsy. Twenty-eight had pure petit mal spells; 18 had grand mal seizures, and 39 had a combination of both types of seizures. Seventy-seven of the patients ranged in age from 2 to 14 years and 8 from 14 to 21 years. The patients were observed for periods varying from two months to five years. The seizures were controlled in 38 per cent and improved in 20 per cent. These drugs were more effective in controlling petit mal than grand mal seizures. There was no difference in the results in idiopathic and organic epilepsy.

Penicillin in Early Congenital Syphilis.—On the basis of reports in the literature and his own studies, Barker suggests administration of 50,000 Oxford units of the aqueous solution of sodium penicillin per pound of body weight at three hour intervals over a period of fifteen days, totaling one hundred and twenty doses. It would probably be advisable to reduce the initial dosage in debilitated infants on the first day by about one half. Treatment may usually be continued when a febrile or Herxheimer reaction occurs. For patients who show no reduction in serologic titer within six months after treatment or in whom the serologic titer increases or clinical relapse occurs, a second course of treatment can be recommended. The repeated course should double the initial dosage. If this also fails to have beneficial effect on the serologic titer or clinical manifestations, then a third course combining even larger doses with fever therapy will be necessary.

New England Journal of Medicine, Boston

238:754-786 (May 27) 1948

Medicine's Responsibility in the Propagation of Poor Protoplasm. A. S. Johnson.—p. 755.
*Chronic Thyroiditis. S. F. Marshall, W. A. Meissner and D. C. Smith. —p. 758.
Tumors of Salivary-Gland Origin. G. W. Taylor and G. G. Gerecken. —p. 766.
Use of Para-Aminobenzoic Acid in Case of Rocky Mountain Spotted Fever. J. O. Niles and G. C. Bourne.—p. 769.
Allergy. W. S. Burrage.—p. 770.
Carbon Tetrachloride Intoxication.—p. 776.
Malignant Lymphoma, Giant-Follicle Type, of Mesentery of Small Bowel. —p. 779.

Chronic Thyroiditis.—Marshall and his associates report a pathologic and clinical study of cases of chronic thyroiditis in which operation was performed at the Lahey Clinic during the period 1928 to 1946, inclusive. During the eighteen year period 187 cases of chronic thyroiditis were encountered in the pathologic examination of specimens from approximately 25,000 patients requiring thyroidectomy. These cases were classified into three groups on the basis of pathologic changes noted in the excised gland, and the findings were correlated with the clinical course. Clinical diagnosis of chronic thyroiditis is possible. It is possible to distinguish thyroiditis from thyroid cancer in a large number of cases. Treatment is unnecessary in

V 1
194

many cases. When it is necessary to establish a diagnosis or to relieve pressure on the trachea, surgical removal of the isthmus or partial thyroidectomy offers the best method. Myxedema develops with the course of the disease. Operation should be planned to minimize this tendency as much as possible.

Radiology, Syracuse, N. Y.

80:439-568 (April) 1948. Partial Index

Focal Epilepsy: Correlation of Pathologic and Radiologic Findings. D. L. McRae.—p. 439.
*Bone Involvement in Malignant Lymphoma. W. C. Coles and M. D. Schulz.—p. 458.
Tumor Dose in Cancer of Larynx. Charlotte P. Donlan.—p. 463.
Consideration of Roentgen Therapy in Producing Temporary Depilation for Tinea Capitis: New Method. E. P. Pendergrass and J. F. Mahoney.—p. 468.
Practical Aspects of Diagnosis, Treatment, and Prognosis of Hodgkin's Disease and Allied Disorders. H. Jackson Jr.—p. 481.
Nitrogen Mustards: Clinical Use. L. F. Craver.—p. 484.
*Newer Nitrogen Mustards in Treatment of Leukemia. J. H. Burchenal.—p. 494.
Lymphoma of Conjunctiva. M. D. Schulz and P. Heath.—p. 500.
Lymphoid Tumors. H. F. Hare, W. C. Mulry and C. F. Sornberger.—p. 506.
Lateral Intrathoracic Meningocele. G. W. Sengpiel, F. F. Rusicka and E. A. Lodmell.—p. 515.
Roentgen Manifestations in Hodgkin's Disease of Retroperitoneal Lymph Nodes. S. Richman.—p. 521.
Unusual Friedländer's Bacillus Pneumonia Associated with Septicemia: Case Report and Brief Review of Literature. J. G. Bulgria.—p. 526.
Regional Jejunitis: 3 Cases. W. L. Janus.—p. 532.
Accidental Filling of Urinary Tract During Barium Enema: Report of Case. S. P. Perry and W. D. Haden.—p. 539.

Bone Involvements of Malignant Lymphoma.—Coles and Schulz say that in the tumor clinic of the Massachusetts General Hospital, in the ten year period from 1936 through 1945, clinical diagnosis of lymphoma was made in 402 patients. In 313 of these the diagnosis was proved by histologic examination. Twenty-five cases of mycosis fungoides being disregarded, there remain 288 histologically proved cases. The determination of involvement of bone was by means of roentgenograms and at necropsy. In 1 case only was bone involvement found post mortem which had not been previously recognized roentgenologically. Of the entire group of 288 patients, 38, or 13 per cent, had manifest involvement of bone. The spine was the most common site. With the exception of solitary reticulum cell sarcoma of bone, which may be a curable disease, the appearance of bone involvement seems to have no notable effect on the prospect for survival beyond that which is recognized for the various subgroups of the disease. Neither does the time of the appearance of the bone lesion in the course of the disease affect the ultimate prognosis, except in widespread reticulum cell sarcoma, when it tends to occur terminally. The occurrence in reticulum cell sarcoma is somewhat disproportionately high—1 in 4.8 patients, compared to 1 in 8 in Hodgkin's granuloma and in lymphosarcoma and 1 in 16 in Hodgkin's sarcoma. The histologic type of the tumor may influence the occurrence of bony involvement. The treatment of bone lesions has corresponded to that in the treatment of malignant lymphoma in general; that is, one of palliation, the intent being to relieve symptoms as they appear. This may be accomplished by amounts of radiation varying from 600 r to 1,500 r.

The Newer Nitrogen Mustards in Leukemia.—Burchenal says that at the Sloan-Kettering Institute certain nitrogen mustard derivatives have been shown to be effective in prolonging the survival time of mice with leukemia. One of these derivatives has been examined extensively for its therapeutic value against leukemia in man. The therapy of acute leukemia with SK 136 has been unsatisfactory. In chronic myelogenous leukemia SK 136 produced results similar to HN_2, radioactive phosphorus, or roentgen therapy. Although not curative, it seems to be a useful tool in the armamentarium of the clinician. In the majority of cases it offers nothing more than skillfully applied roentgen therapy.

South Carolina Medical Assn. Journal, Greenville

44:155-186 (May) 1948

X-Rays in Treatment of Common Inflammatory Conditions. W. S. Judy and S. H. Fisher.—p. 155.
Management of Infantile Diarrhea and Dysentery. T. D. Dotterer.—p. 158.
Advances in Orthopedic Surgery. G. R. Dawson, Jr.—p. 160.
Epidermal Sensitivity Due to Streptomycin. G. C. Smith.—p. 164.

Surgery, Gynecology and Obstetrics, Chicago

86:641-774 (June) 1948

Healing of Bowel as Influenced by Sulfasuxidine and Streptomycin. E. J. Poth, J. P. McNeill, L. J. Manhoff Jr., W. B. King and J. G. Sinclair.—p. 641.
Intestinal Intubation in Small Bowel Distention and Obstruction: Further Experiences with Single Lumen Mercury Weighted Tube and Analysis of Complications. F. I. Harris and M. Gordon.—p. 647.
Characteristics of Mixed Tumors of Parotid Gland Growing in Vitro. B. V. Favata.—p. 659.
Use of Polythene Film as Dural Substitute: Experimental and Clinical Study. M. H. Brown and J. H. Grindlay.—p. 663.
Effects of Absorbable Foreign Substances on Bowel Anastomosis. H. Lauffman and H. Method.—p. 669.
*Toxemia Superimposed on Prepregnant Hypertension Treated by Splanchnicectomy. M. M. Peet, E. M. Isberg and R. C. Bassett.—p. 673.
Clinical Study of Effect of Intercostal Nerve Block with Nupercaine in Oil Following Upper Abdominal Surgery. R. S. McCleery, R. Zollinger and N. E. Lenahan.—p. 680.
*Experimental Study of Comparative Efficacy of Heparin and Dicumarol in Prevention of Arterial and Venous Thrombosis. W. B. Kiesewetter and H. B. Shumacker Jr.—p. 687.
Carcinoma of Pancreas: Clinicopathologic Survey. G. B. Silver and Ruth K. Lubliner.—p. 703.
Transplantation of Peroneus Longus to Anterior Tibial Insertion in Poliomyelitis. R. E. Ingersoll.—p. 717.
*Tumors of Breast: Preoperative Roentgenography. J. Gershon-Cohen and P. J. Hodes.—p. 723.
Neurovascular Complications from Malposition on Operating Table. H. C. Slocum, K. C. O'Neal and C. R. Allen.—p. 729.
Various Types of Diaphragmatic Hernia Treated Surgically: Report of 430 Cases. S. W. Harrington.—p. 735.

Splanchnicectomy in Toxemia Superimposed on Prepregnant Hypertension.—According to Peet a new therapeutic approach to the problem of toxemia superimposed on prepregnant hypertension has been tried at the University of Michigan Hospital during the past five years. Bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy has been performed in 5 such cases. This surgical treatment is aimed directly at the underlying hypertensive disease, for it is believed that the complicating toxemia is a consequence of the preexisting hypertensive state. In 2 cases the results have been excellent; after operation in both, the toxemia disappeared, normal blood pressure levels were achieved, living infants were obtained, and normal blood pressure has persisted since delivery. In the remaining 3 patients the operation exerted no influence on the toxemia, but in 1 of the patients the blood pressure levels following delivery have been significantly decreased as compared with the prepegnant levels.

Comparative Efficacy of Heparin and "Dicumarol" in Prevention of Thrombosis.—Kiesewetter and Shumacker carried out experiments on healthy mongrel dogs ranging in weight from 5 to 20 Kg. Two hundred and twenty-eight veins and 177 arteries were traumatized and subsequently examined for thrombosis. Thrombosis occurred on the first or second day following injury to the vessels. "Dicumarol" and heparin appeared equally effective in reducing the incidence of venous thrombosis. Anticoagulant therapy was more efficacious in preventing arterial than venous thrombosis. With doses of "dicumarol" adequate ordinarily to maintain a low prothrombin level and of heparin generally inadequate to maintain a constantly prolonged coagulation time, statistically superior results were obtained with heparin in preventing thrombosis of injured small arteries. The results were not statistically different in preventing thrombosis in larger arteries.

Roentgenography in Tumors of Breast.—According to Gershon-Cohen and Hodes roentgenography of breasts for the diagnosis of early cancer is especially valuable in that small group of cases, possibly less than 10 per cent, in which both the clinical examination and transillumination have failed. Routine roentgenography is to be recommended in the diagnosis of mammary disease. Small malignant lesions in fat breasts can often be demonstrated when their presence is not otherwise suspected. Abnormalities and other diseases of the breast can also be studied and, while there are limitations to accurate diagnosis, these limitations can be reduced by better acquaintance with the roentgen examination. The malignancy or benignancy of a growth occasionally can be determined by its roentgenographic appearance. A survey roentgen examination of the chest and skeleton might well be recommended before operation for all patients suspected of having malignant disease.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted. Single case reports and trials of new drugs are usually omitted.

British Journal of Dermatology and Syphilis, London

60:159-194 (May) 1948

*Treatment of Lupus Vulgaris with Large Doses of Calciferol: Clinical and Biochemical Appraisal: Part 1.—Clinical. J. T. Ingram and S. T. Anning.—p. 159.
Calciferol for Lupus and Other Conditions. D. E. Macrae.—p. 168.
Calciferol in Treatment of Tuberculosis. Suzette Gauvain.—p. 174.
Histologic Changes in Lupus During Calciferol Treatment. W. Freudenthal.—p. 178.
Three Cases of Hodgkin's Disease with Predominantly Cutaneous Localization. L. Van der Meiren.—p. 181.

Calciferol in Lupus Vulgaris.—Ingram and Anning believe that more than 70 per cent of patients with lupus can be cured clinically in twelve to eighteen months by daily ultraviolet light baths to the whole body, combined with improved living conditions, particularly dietetic and environmental improvements. Calciferol has a striking effect on certain cases of lupus. The authors review observations on the effects of treatment with calciferol in 158 cases of lupus and 28 other cases. Four of the 158 patients with lupus have been cured and 23 have been improved, whereas in the other 131 cases the results have been negligible. Toxic effects have been observed in 30 patients, and in an additional 25 per cent gross disturbances developed in the calcium metabolism. A high percentage of those with diffusible calcium also show impaired renal function. The permanency of this damage is not known at present. In 1 child the renal function was only 40 per cent of normal thirty-four weeks after cessation of treatment with calciferol. In general, the experience of these authors with calciferol has not been very favorable. They do not believe that it will replace treatment with light in lupus and that its definite evaluation will require considerably more time. In sarcoidosis the results obtained with calciferol have been rather good, and good effects have been obtained also in erythema induratum and in scrofuloderma, but in tertiary syphilis the results were not good. The incidence of chilblains was not reduced during calciferol therapy.

British Medical Journal, London

1:917-964 (May 15) 1948

Etiology, Diagnosis, Treatment of Early Vitamin-Deficiency States. Z. A. Leitner.—p. 917.
*Treatment of Neurosyphilis with Penicillin. J. P. Martin.—p. 922.
Case of Acute Porphyria. E. Petrie.—p. 926.
Case of Acute Mononitrobenzene Poisoning. J. D. N. Nabarro.—p. 929.
Heterotopic Ossification of Appendicular Mucocele. I. Juvara and U. Borcescu.—p. 931.

Penicillin in Neurosyphilis.—Martin reviews observations on 24 patients with neurosyphilis who were treated with penicillin. This number included 8 patients with dementia paralytica, 5 with tabes, 2 with optic atrophy and 9 with meningovascular syphilis. Penicillin was given by the intramuscular route only. Sodium penicillin was used for most of the cases, and in recent times the crystalline form whenever obtainable. In the early days the total amount given in each course was 2,000,000 Oxford units. This was soon increased to 3,000,000 and then 4,000,000; for the last two years the course has been standardized at 5,000,000 units. Although he realizes that longer observation is necessary, the author concludes that penicillin alone is sufficient in most cases of neurosyphilis. Whether it is adequate for the most acute cases of general paralysis of the insane the experience of this series does not show. If, with the possible exception of such cases, the patient can be kept under observation after treatment and penicillin repeated if necessary, malaria will seldom be called for, and, if malaria is used at all, risks which were necessary before need not now be taken.

Journal of Royal Army Medical Corps, London

90:93-132 (March) 1948. **Partial Index**

Early Days of Army Psychiatry. R. Rosie.—p. 93.
*Pathology of Liver in Deaths from Thermal Burns. A. P. Prior.—p. 101.
Diphtheria in Army in United Kingdom: Study of Its Complications. R. G. Paley and S. C. Truelove.—p. 109.

Pathology of Liver in Deaths from Thermal Burns.—Prior gives an account of the lesions seen in the livers of 35 men who died as the result of thermal burns. The nature of the cellular changes could be coupled with the topical therapy. Those treated with tannic acid showed central lobular necrosis. Intranuclear and intracytoplasmic inclusions were not found. Those treated with sulfonamide drugs showed fatty degeneration. No specific changes were found in those who received only bland treatment in the form of applications and baths of isotonic sodium chloride solution.

Journal of Tropical Medicine and Hygiene, London

51:89-110 (May) 1948

Diagnosis of Rectal Schistosomiasis. C. V. Meeser, W. F. Ross and D. M. Blair.—p. 91.
Cholera in Egypt: Laboratory Diagnosis and Protective Inoculation. M. A. Gehar and M. Makkawi.—p. 95.
Studies in Tropical Ulcer: Part III.—The Insect Vector. K. Hare.—p. 99.

Lancet, London

1:737-776 (May 15) 1948

Psychiatry as Applied to Occupational Health. D. Stewart.—p. 737.
Is Rheumatism Virus Disease? M. Gordon.—p. 740.
*Rubella in Pregnancy as Etiologic Factor in Stillbirth. C. Swan.—p. 744.
*Maternal Measles, Mumps, and Chickenpox as Cause of Congenital Anomalies. M. J. Fox, E. R. Krumbiegel and J. L. Teresi.—p. 746.
Avulsion Fracture of Lesser Tuberosity of Humerus: Report of Case. A. T. Andreasen.—p. 750.
Exophthalmic Ophthalmoplegia Treated with Prostigmin. C. F. Critchley and A. J. Cameron.—p. 751.

Rubella in Pregnancy and Stillbirths.—Swan says that the role played by rubella in the production of congenital malformations is now well known. Rubella appeared also to be associated with a high incidence of stillbirths. In 1946 the author made a survey of the cause of about a third of the stillbirths recorded in South Australia in the seven years 1939 to 1945, with special attention to the incidence of infectious diseases during pregnancy. There were 2,156 stillbirths registered from 1939 to 1945; questionnaires were sent to 1,265 of the mothers, and 760 replies were received. There were 16 instances (1 doubtful) of maternal rubella during pregnancy, and in 13 of these the infection took place during the first four months of pregnancy. Though various other infections had been contracted by these mothers in pregnancy, rubella was the only one which showed this particularly high incidence in the early months. It is suggested that rubella may be a factor in the causation of stillbirths by damaging the embryo early in pregnancy.

Maternal Measles, Mumps and Chickenpox as Cause of Congenital Anomalies.—Fox and his associates say that the reporting of congenital anomalies in babies born of pregnancies in which the mothers had had rubella has naturally raised the question whether other infectious diseases, particularly those due to a virus, may cause similar defects. All notifications of measles, mumps and chickenpox to the Milwaukee Health Department from 1942 to 1945 were examined, and as many as possible of the married women who had had these diseases were interviewed to determine the incidence of congenital anomalies among their offspring. The incidence of anomalies in this group of 665 children was 0.9 per cent. Of 33 live children born to the same number of married women who had measles, mumps or chickenpox while pregnant, 1 had a congenital anomaly. One pregnancy ended in spontaneous abortion in the second month. None of 22 children born of pregnancies complicated by mumps and none of 4 children born of pregnancies complicated by chickenpox showed congenital defects, but 1 of 7 children born of pregnancies complicated by measles had a unilateral harelip. The reports of other workers on anomalies following maternal rubella in pregnancy indicate an over-all incidence about fifteen times the expected rate of 0.9 per cent, and in the case of mothers who had had rubella in the first four months of gestation more than eighteen times the expected rate. The authors are aware that this series is too small for definite conclusions to be drawn.

Tubercle, London

29:97-120 (May) 1948

Modern Methods of Culturing Mycobacterium Tuberculosis, with Special Reference to Dubos Technic. A. Roberts.—p. 97.
Bilateral Active Pulmonary Tuberculosis Treated with Artificial Pneumothorax and Thoracoplasty: Review of 29 Cases. G. P. Maher-Loughnan.—p. 101.
Autopsy Findings in Boeck's Sarcoid. H. J. Ustvedt.—p. 107.

Klinische Wochenschrift, Heidelberg

26:129-160 (March 1) 1948. **Partial Index**

Iso-Immunization as Cause of Fetal Erythroblastosis (4 Cases Produced by Rh Factor). P. Peau.—p. 132.
Modification of Action of Acetylcholine by Ferment Decomposition of Histamine by an Antihistamine and by Vitamin B1. G. Stüttgen. —p. 136.
*Allergy and Gastric Diseases. B. Fang.—p. 141.
Vestibular Reaction Elicited Acoustically. J. Tonndorf.—p. 149.

Allergy in Patients with Stomach Disorders.—Fang points out that at the medical clinic of the University of Heidelberg 729 patients with gastric disturbances who had either an ulcer or severe gastritis were subjected to cutaneous tests with various types of foods. Over 60 per cent of the patients, or 441, gave positive allergic reaction to one or several foods. The substances producing cutaneous allergic reactions were, in order of decreasing frequency, meat, milk, egg yolk, barley, oats, vegetables, egg white, rye, fish and wheat. Only 29, or 17 per cent, of 170 patients without gastric disturbances gave positive reaction to the food substances. The author believes that the considerable difference in incidence of allergic reactions between the groups with and without gastric disturbances indicates a positive correlation between gastric and allergic disturbances. The relative rarity of polyvalent allergy indicates that allergy is less often a sequel than a causal factor in gastric disturbances. Allergic reaction of the gastric mucosa to the substance that had elicited positive reaction in cutaneous test was indicated by subjective symptoms in 12 of 15 cases. Other authors who studied the gastric secretion in order to ascertain an allergic reaction of the gastric mucosa did not succeed in demonstrating allergy in this way. In 8 patients with ulcers and in 7 with gastritis, the authors were able to employ desensitization to the offending substance. For two weeks the substance was eliminated from the diet, and this together with a rest cure usually improved the subjective symptoms. Then desensitization was instituted by giving twice weekly a subcutaneous injection of 0.1 cc. of a concentration of the specific allergen. The first concentration was often as low as 1:106, but in the course of five to eight injections the concentration was increased to 1:10. Then followed oral desensitization, beginning with one-half teaspoonful of the allergen (1:200) in a cup of broth, milk or gruel. The oral dose was slightly increased every day. After six weeks, 12 or 17 patients were completely free from symptoms and the others showed great improvement. The desensitization exerts no influence on psychic or other factors that may play a part in the development of the gastric disturbances.

Nordisk Medicin, Stockholm

38:819-870 (April 23) 1948. **Partial Index**

*Medical Interview and Personal Relation Between Physician and Patient. J. C. Whitehorn.—p. 819.
*Thymol Reaction in Acute Infectious Diseases. K. Iversen and F. Raaschou.—p. 824.
Transvesical Prostatectomy in One Stage. K. Liavaag.—p. 828.
Prostatic Hypertrophy and Cancer of Prostate (1910-1938). A. Hvoslef. —p. 832.
Treatment of Tendinous Panaritia with One Incision, Immobilization and Penicillin Intramuscularly. I. Andersen.—p. 839.

Medical Interview and Personal Relation Between Physician and Patient.—Whitehorn stresses the importance of the physician's understanding and handling of the emotional relation between patient and physician. Through emotional reactions or psychoneuroses man himself is a biologic cause of disease. Skill and poise in interviewing enable the physician to gain an insight into the patient's personal problems and evaluate them as the cause of medical complaints or complicating factors in organic disease. In the interview, conducted not only for the purpose of acquiring information about present and earlier symptoms but also for the revelation of current attitudes, discussion of occupation and home life, is often revealing. Acquaintance with the different stages of emotional development provides the key to the understanding of personal reactions otherwise difficult to interpret and affords guidance in therapeutic strategy. The emotional relationship with the physician in which the patient may become involved, the transference relationship, can be modified by control of the frequency, duration and intimacy of the interviews and by the patient's intercourse with other persons.

Thymol Reaction in Acute Infectious Diseases.—Iversen and Raaschou say that the thymol test, applied in 393 patients with various acute infectious diseases and in 88 normal persons, gave positive results in measles, infectious mononucleosis and hepatitis. They conclude that the thymol reaction can hardly be considered as a hepatic function test but is rather to be regarded as an expression of changes in the serum proteins due to different virus infections. Whether the changes are qualitative or quantitative is not known.

Revista Españ. de Pediatría, Zaragoza

4:1-150 (Jan.-Feb.) 1948. **Partial Index**

*Value of Mester's Reaction and Its Modification in Diagnosis of Rheumatic Disease. J. Puig Serrate and A. Barber Orña.—p. 32.
*Treatment of Infantile Paralysis in Acute Period. V. Sanchis Olmos. —p. 133.

Mester's Test in Diagnosis of Rheumatic Fever.—Serrate and Barber Orña modified Mester's test by using a 1:1,000 aqueous solution of sodium salicylate. By this modification the pain of the intradermal injection is diminished and the results of the test are as specific as those of Meyer's original test. The test is of great diagnostic value and is specific. Blood for the test is to be taken three times in both the original and the modified test, that is, before the test and again thirty and sixty minutes after it. The number of leukocytes drops after thirty and sixty minutes. The authors obtained positive results in 14 of 17 children with clinical symptoms of rheumatic disease. The test is specific even in cases in which rheumatic disease coexists with either tuberculosis or syphilis.

Treatment of Infantile Paralysis.—The number of cases of poliomyelitis seen in Spain by the author since 1941 is about 1,000. The author found that muscular spasm is independent of paralysis. It is present in all cases of poliomyelitis. Acute muscular spasm is of better prognosis for functional muscular recovery than subacute spasm. Muscular blockage or pseudoparalysis, alone in antagonistic muscles and in combination with spasm in certain antagonistic muscles, muscular incoordination in either spastic or pseudoparalytic muscles and disturbances of the peripheral structures are frequent. Kenny's treatment is of value. The technic for early and late application of warm compresses, physical therapy, manual correction of muscular deformities and muscular reeducation is described in detail. The treatment, which should be given only by physicians trained in the proper technic, prevents talipes equinus, flexion-abduction of muscles, obliquity of pelvis, scoliosis and certain aponeurotic retractions. Sequels due to destruction of motor neurons are incurable.

Wiener medizinische Wochenschrift, Vienna

98:181-200 (May 1) 1948. **Partial Index**

Causes and Mode of Origin of Variations of Constitution in Man. L. Borchardt.—p. 181.
Hemostyptic Effect of Artificial Cutaneous Emphysema in Hemorrhage of Lung. F. Höglinger.—p. 183.
*Congenital Formation of Cavities of Cerebrum with Contribution to Encephalography of Porencephalous Defects in Children. H. Stech. —p. 184.

Congenital Porencephaly in Children.—Stech reports a rare case of genuine porencephaly in a girl aged 4½ years. The condition was demonstrated roentgenologically in vivo and established on necropsy. After a presumably normal birth the child was given hospital treatment for debility for three months. She never learned to speak. Because of emaciation and mental deterioration the child was readmitted to the hospital. She was apathetic and subject to convulsions. Encephalography revealed a porencephalous defect in the region of the left frontotemporal-parietal lobe triangle, communicating with the lateral ventricle and with the subarachnoid space on the same side. The defect was of Guttmann's porus communicans type. Five days after the encephalography the child became lethargic, and death occurred after repeated convulsions. It is suggested that the porencephaly could have been caused by trauma to the brain during delivery. Encephalography appears to be adequate in demonstrating the lesion in doubtful cerebral disturbances.

Book Notices

Vitamins and Hormones: Advances in Research and Applications. Vol. V. Edited by Robert S. Harris, Professor of Biochemistry of Nutrition, Massachusetts Institute of Technology, Cambridge, Mass., and Kenneth V. Thimann, Professor of Plant Physiology, Harvard University, Cambridge, Mass. Cloth. Price, $7.50. Pp. 478, with illustrations. Academic Press, Inc., 125 E. 23rd St., New York 10, 1947.

This volume is the fifth in an annual series which is serving the biochemist, physiologist and thoughtful physician by keeping him abreast of recent progress in two fields in which research is advancing with great rapidity. The discussions are detailed and have an international character, since several of the reviews have been prepared by European contributors. Although most of the principal advances in the vitamin field are adequately discussed, two reports deserve particular attention. The discussion of the physiologic availability of the vitamins by Melnick and Oser has many clinical implications and deserves attention by all concerned with problems in nutrition. The review on the physiologic effects of the pteroylglutamates in man summarizes in detail our knowledge of the actions and uses of folic acid.

The section dealing with hormones presents discussions only on selected topics. Of particular interest are the reviews on the use of androgens in women and the clinical uses of testosterone in the male. Heller and Maddock in this latter review point out that the "male climacteric" is rather infrequent and has been confused with a psychosomatic syndrome in neurotic old men. A diagnosis of the "male climacteric" should not be made without demonstration of elevated urinary gonadotropins. Testosterone therapy is of real benefit only in true androgen deficiency.

Other sections relating to hormones discuss the growth and adrenocorticotropic hormones, the effects of exogenous estrogens on the male mammal and the biology of antithyroid agents. The reviews are all well written. The entire volume reflects care on the part of the editors. Tables, charts and illustrations are used effectively.

The Natural History of Disease. By John A. Ryle, M.A., M.D., F.R.C.P., Professor of Social Medicine in the University of Oxford, Oxford, England. Oxford Medical Publications. Second edition. Cloth. Price, $7.50. Pp. 184, with illustrations. Oxford University Press, 114 Fifth Ave., New York 11; Amen House, Warwick Sq., London, E. C. 4, 1948.

American readers will benefit both from the style and the content of this book. In addition to a few essays on medical education in the broadest sense, there are nearly thirty chapters in which the natural history of angina, gastrointestinal syndromes, pyogenic infections and other common clinical disorders is illustrated by pithy case histories. Three new essays have been added since the first edition was published in 1936. Those on pyogenic infections have not been revised to deal with the modification of the natural history by antibiotics.

These stimulating discussions, while written by an internist and consultant, emphasize precisely those aspects of disease which are most important for the family practitioner and the young physician. Some of the therapy and clinical physiology will be strange to American readers, but the fine points of bedside and office diagnosis, the discussions of the role played by environment and personality in causing or coloring disease and the clear concise paragraphs make this a useful addition to the physician's library.

Handbook for Physicians. Loose-Leaf. Paper. Pp. 168. Commonwealth of Massachusetts, Department of Public Health, State House, Boston 33, 1947.

This is a looseleaf continuous ring binder book in paper covers which has been published annually for several years by the Health Department of the Commonwealth of Massachusetts. It contains 160 pages of information which will help doctors taking fullest advantages of the services of the Massachusetts State Department of Health, including clinics, laboratory services, hospital relationships, information about laws and regulations and numerous details of information which will help to smooth the relationship between the public health and the private practice aspects of medical service to the people of Massachusetts. Although not so classified, it constitutes an outstanding piece of practical public relations work on the part of the department.

Neurology of the Ocular Muscles. By David G. Cogan, M.D., Associate Professor of Ophthalmology, Harvard Medical School, Boston. Cloth. Price, $6. Pp. 214, with 69 illustrations. Charles C Thomas, 301-327 E. Lawrence Ave., Springfield, Ill., 1948.

The author has made an attempt to correlate the clinical manifestations of disturbances of the ocular motor system with its neuroanatomic and neurophysiologic structure by presenting the state of the present knowledge of the clinical physiology of the ocular motor system and making clear the conclusions that can safely be drawn from the facts available. The data in this text are arranged according to objective signs rather than disease entities, as neuro-ophthalmology is concerned primarily with localization of disease and only secondarily with the nature of the underlying process. The first section of the book concerns the anatomy and physiology of the ocular muscles. The next section is on the anatomy of the nerves running to the extraocular muscles. A third section pertains to the supranuclear connections of the ocular motor system. The last two sections are concerned with the pupil and nystagmus. The chapter on nystagmus is probably the most comprehensive article on this subject in the English language. The book is profusely illustrated and contains a comprehensive bibliography of 825 references in many languages. The contents will be found of great interest to both practicing ophthalmologists and neurologists.

The 1947 Year Book of Neurology, Psychiatry and Neurosurgery. Neurology. Edited by Hans H. Reese, M.D., Professor of Neurology and Psychiatry, University of Wisconsin Medical School, Madison, Wisconsin, and Mabel G. Masten, M.D., Associate Professor of Neuropsychiatry, University of Wisconsin Medical School. Psychiatry. Edited by Nolan D. C. Lewis, M.D., Director, New York State Psychiatric Institute and Hospital, New York. Neurosurgery. Edited by Percival Bailey, M.D., Professor of Neurology and Neurological Surgery, University of Illinois, Chicago. Fabrikoid. Price, $3.75. Pp. 702, with 115 illustrations. The Year Book Publishers, Inc., 304 S. Dearborn St., Chicago 4, 1948.

This handbook is the forty-eighth annual publication made by the Year Book Publishers. The authors are excellent clinicians, and because of this the material outlined is extremely practical and valuable. The neurologic part of this book contains 245 pages of review of most all the publications in 1947 which the authors considered important. It includes articles on anatomy, physiology and pathology, convulsive disorders and diseases of the central, peripheral and autonomic nervous systems as well as the vascular and muscular structures. Special diagnostic and therapeutic measures are discussed. The psychiatric aspect consists of 174 pages of practical psychiatry and psychoneuroses. The neurosurgical part is a relatively new addition to this handbook. It contains 221 pages of reviews of various neurosurgical papers published in 1947. This is an excellent book of reviews.

The Maryland Medical Care Program: A Report by the Staff of the Subcommittee on Medical Care, Committee on Administrative Practice, American Public Health Association. By Howard M. Kline, Ph.D., Milton Terris, M.D., Cozette Happey and Nathan A. Kramer. Paper. Pp. 151, with illustrations. American Public Health Association, 1790 Broadway, New York, 1948.

This study is one of a series being prepared by the staff of the Subcommittee on Medical Care of the American Public Health Association. It describes critically the procedures and arrangements by which medical services are provided to the indigent and medically indigent in the state of Maryland.

Maryland has a unique system for caring for the medical needs of indigent and medically indigent persons. Instead of the usual three way division (state-city-county), the administration of a statewide program has been placed in the hands of the state department of health, with actual operation under a "bureau of medical services." This bureau is empowered to contract with physicians, dentists and hospitals for their services. To carry out this program, the Medical Care Act of 1945 provided for an advisory state council on medical care to include fourteen members representing the several professions and the official organizations directly affected by the program.

From the beginning, every effort was made to enlist the cooperation of the medical profession. A general policy of decentralization has been carried on to the extent that each county makes most of its own important decisions. Such decisions are generally made through a county committee on

medical care which includes representatives of the medical and dental societies, as well as officials of the county agencies. Patients are entitled to home, office and hospital calls and have free choice of physicians. Payments to physicians are made on a fee for service basis in accord with a fee schedule arrived at in consultation with the medical profession.

When a physician finds a patient unable to pay for services, the two together make out an application which the patient sends to the county health department. If the patient is indigent or medically indigent, certification is made by the health officer who issues an identification card to the patient. This card is presented to the physician at each call, and the physician bills the health department at the end of the month.

This report of the subcommittee provides an interesting insight into the problems which arose during the development of the Maryland medical care program. It outlines the program as it is now functioning and, in addition, provides a valuable, detailed analysis of the experience during the period from July 1945 to September 1946. The experience of the program as shown by the report seems to indicate that the means test can be applied successfully and that special provision can be made for care of the medically indigent as well as the indigent.

The only criticism voiced by the representatives of the American Public Health Association making the study is that "too many issues are resolved by requesting the faculty (medical and chirurgical faculty of Maryland) for advice or by urging that the county medical societies be canvassed for their recommendations." They go on to state, "To the medical members of the [advisory] Council the terms 'county advisory committee' and 'county medical society' are practically synonymous." It may well be that these are not criticisms but rather the basic reasons for the singular success of the Maryland medical care program. This study should be "must" reading for every state medical society officer interested in setting up a medical care program for the indigent and medically indigent.

Health Center Buildings. By Harry E. Handley, M.D., Assistant Director, Division of Public Health, The Commonwealth Fund. Paper. Price, 50 cents. Pp. 48, with illustrations. The Commonwealth Fund, 41 E. 57th St., New York 22. 1948.

Since 1930 the Commonwealth Fund has been concerned with the construction of eight health center buildings to house local health departments and their activities. This pamphlet presents experiences in seven of these health centers—four in Tennessee and three in Mississippi—with regard to location, space requirements, architectural design and use of the building. Nineteen pages are devoted to pictures of the health centers, together with their floor plans. Under this program it was agreed that the activities initiated during the "demonstration period" with financial assistance from the Fund would be continued with state and local tax money. A modified Georgian style was adopted by the Commonwealth architects, combining utility, fire resistance, low maintenance cost and pleasing appearance. An effort was made at each building site to take advantage of natural features. At the time each of these buildings was planned the official health service was essentially preventive and educational in character. Various local groups, interested in the educational facilities provided by the buildings, were invited to make use of them. To encourage their use by practicing physicians, the Fund made small initial contributions to several of the health centers for the purchase of medical books and magazines. In most of the areas the local medical society uses either the library or the auditorium for its meetings. In the absence of local hospitals, provision was also made for diagnostic laboratory facilities for use by the practicing physicians. From experience gained in the construction and use of these buildings definite concepts of the requirements for a health center building have been developed by the Fund staff. In view of the increase in local health centers through the Hospital Survey and Construction program of the Hill-Burton Act and the bill sponsored by the National Congress of Parents and Teachers for financing local health units, this demonstration on health centers affords basic study material for all groups interested in the extension of better health and medical service, particularly in the rural areas.

The Epithelia of Woman's Reproductive Organs: A Correlative Study of Cyclic Changes. By George N. Papanicolaou, M.D., Ph.D., Professor of Clinical Anatomy, Cornell University Medical College, New York, Herbert F. Traut, M.D., Professor of Obstetrics and Gynecology, University of California Medical School, San Francisco, and Andrew A. Marchetti, M.D., Associate Professor of Obstetrics and Gynecology, Cornell University Medical College, New York. Cloth. Price, $10. Pp. 55, with 24 illustrations. The Commonwealth Fund, 41 E. 57th St., New York 22; Oxford University Press, Amen House, Warwick Sq., London, E. C. 4, 1948.

Here is the fundamental textbook on the Papanicolaou method for determining the presence of cancer. The book reports studies made since 1937 involving examination of the organs of 233 women and covering examination of more than 10,000 specimens. The organs concerned are the ovaries, tubes, various portions of the uterus and vagina. After a consideration of the problems involved in menstruation, chapters are devoted to the epithelium of the tissues concerned and to the cytology of various secretions and excretions. The studies are correlated with the menstrual cycle. Of greatest value in the work are a series of more than twenty magnificent colored plates and a final production indicating in color the cytology of the normal menstrual cycle. The book is invaluable for every physician who attempts this type of work.

Basic Facts of Health Education for Members of the Medical, Pharmaceutical and Nursing Professions. Selected Articles from the Ministry of Health Bulletins which have appeared in the Pharmaceutical Journal, 1944-1947. Boards. Price, 7s.6d. Pp. 193. The Pharmaceutical Press, 17 Bloomsbury Square, London, W.C.1. [1948].

This book is a compilation of selected items from the Bulletin of the British Ministry of Health which have appeared in *The Pharmaceutical Journal*. In 1943, the Pharmaceutical Society suggested to the Ministry of Health that means should be established so that pharmacists might obtain first hand knowledge of matters engaging the attention of the Ministry of Health. The issue of a bulletin at regular intervals was decided on, and the Pharmaceutical Society offered to publish these bulletins in its journal. The first of these appeared in January 1944 and others were published subsequently at quarterly intervals.

The fifty-two bulletins published in this volume cover a wide variety of topics starting with positive health and including such subjects as dental disease, importance of pure water, food poisoning, cancer, several on the menstrual function, a number on the common contagious diseases of childhood, dust in the home and factory, BCG vaccination, several on the venereal diseases, blood banks and plasma, and geriatrics. Each of the bulletins is brief, averaging from 3 to 4 book size printed pages. The book is well indexed. The principal interest attaching to these bulletins for American readers is the background which they give of the British attack on health education. Medical and pharmaceutical cooperation is being developed in the United States; this book may contain suggestions as to how it can be most constructively carried forward, bearing in mind differences between British and American conditions.

Tomorrow's Food: The Coming Revolution in Nutrition. By James Rorty and N. Philip Norman, M.D. Foreword by Stuart Chase. Cloth. Price, $3.50. Pp. 258. Prentice-Hall, Inc., 70 Fifth Ave., New York 11. 1947.

Obviously Rorty's enthusiasm ran away with Dr. Norman's science. In addition to many inaccuracies this book is studded with ill founded generalizations concerning the American physician, his British colleague, the National Research Council's Food and Nutrition Board, and the Council on Foods and Nutrition of the American Medical Association.

The text of the book is concerned with a back to nature movement in nutrition with which almost all nutritionists are in accord; however, the authors fail to realize that this can be accomplished only by public education and guidance and not by ax-swinging iconoclasts.

Among some of the more blatant passages are the following:

In reference to the National Health Insurance Act in Britain, "An increase of sickness among his panel patients brought no increase of income to the doctor. It meant only more work and less sleep; whereas less sickness meant more leisure for study and recreation, as well as a better chance to supplement his income by attending, on a fee for service basis, the middle class and upper class patients not covered by the Act. Hence, having thus acquired a vested interest in health, he proceeded to do something about it."

138
48

"These are the adrenal glands, than which there is no richer source of vitamin C in either animal or plant tissues." [Except green peppers, red peppers, parsnip greens, guavas, rose hips, and West Indian cherries, to mention but a few.]

"In the Mongolian idiot, the gyrus cingulum of the brain is missing. . . ." The authority in this case must be Mr. Rorty or Godey's *Lady Book*.

"Mass production of eggs—which gives us nonfertile eggs, devoid of an essential hormone."

"Homogenized milk! Can this be an oversight on the part of Divine Providence—did He forget to place an egg beater in the cow's udder?"

"All that one could be sure of was that since the food industry paid the piper, it would insist, in the end, on calling the tune. Most of the members of the Food and Nutrition Board were also connected with or dependent upon one or several of these various [industry-supported] committees and foundations. Hence when the industry supported Nutrition Foundation caught cold, the A. M. A.'s Food and Nutrition Committee sneezed; . . ."

These statements typify the book. While there is much material in this book with which no modern nutritionist would disagree, it is inextricably intermingled with nonsense and wild accusations.

British Surgical Practice. Volumes I and II. Under the General Editorship of Sir Ernest Rock Carling, F.R.C.S., F.R.C.P., Consulting Surgeon, Westminster Hospital, London, and J. Paterson Ross, M.S., F.R.C.S., Surgeon and Director of Surgical Clinical Unit, St. Bartholomew's Hospital, London. Cloth. Price, each volume, $15; $125, per set of 8 volumes and Index. Volume I, pp. 536, with 228 illustrations. Volume II, pp. 575, with 318 illustrations. C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3; Butterworth & Co., Ltd., 4-5 Bell Yard, Temple Bar, London, W. C. 2. 1947 (Volume I) and 1948 (Volume II).

These are the first two volumes of an eight volume survey of surgical practice in Great Britain. The editors state in the introduction that this is not intended for the experts. Nor is it intended for the medical student. Primarily, it is a thoroughly practical review of British surgery designed for surgeons with limited access to libraries. Under the supervision of the editors an imposing roster of contributors have compiled these volumes. A simple straightforward account of each subject has successfully eliminated the often cumbersome erudition which frequently characterizes overseas expositions of surgical material. The arrangement of contents is encyclopedic.

Each author is an authority in his field and the material is presented in matter of fact style. Marginal annotations, paragraphic headings and pre-chapter outlines render the information readily accessible. Suitable references are appended to each chapter. Those familiar with previous publications in the field of surgery emanating from England will recognize a distinct superiority in this enterprise. There is an absence of the usual deadwood and little use of vague eponymic terms. It was a little surprising to run across a rather fulsome description of Sclavo's serum for anthrax, although penicillin was somewhat cautiously recommended instead.

The books are amply illustrated. It is difficult to recommend their purchase in this country where medical libraries and medical literature are widely distributed. An undertaking of this type is expensive and subsequent revisions to keep pace with rapidly expanding fields of medicine and surgery may render the project a poor investment. However, the purpose thus far seems to be satisfactorily accomplished.

Human Neuroanatomy. By Oliver S. Strong and Adolph Elwyn, Associate Professor of Neuroanatomy, College of Physicians and Surgeons, Columbia University, New York. Second edition. Cloth. Price, $6. Pp. 442, with 336 illustrations. Williams & Wilkins Co., Mount Royal and Guilford Aves., Baltimore 2, 1948.

A review of the first edition of this excellent textbook was published in THE JOURNAL in 1943, in volume 122, p. 1214. A chapter on peripheral and segmental innervation has been added, which, curiously enough, starts with the second cervical but says not a word about the cranial nerves. The other major change is a much enlarged chapter on cerebral circulation. It is gratifying to encounter, among other things, the veins of Trolard and Labbé in a student's textbook. There is a tendency to make revisions less thorough than they might be. One can only hope that future editions will include allusion to the work of J. Z. Young or P. Weiss on nerve fibers, to that of Caspersson and his school on the cytochemistry of the nerve cell and to that of Snider and others on the cerebellum. Even as it is, the reader will find this book with its well selected and carefully prepared bibliography highly useful and instructive.

Textbook of Gynecology. By Emil Novak, M.D., F.A.C.S., Assistant Professor of Gynecology, The Johns Hopkins Medical School, Baltimore. Third edition. Cloth. Price, $8. Pp. 742, with 484 illustrations. Williams & Wilkins Co., Mount Royal and Guilford Ave., Baltimore 2, 1948.

The first edition of this book bore the title "Gynecology and Female Endocrinology" and, whereas the second and this edition do not include "Female Endocrinology" in the title, this subject still forms a large and important part of the book. As in the previous editions the author does not discuss operative procedures but takes up the anatomy and physiology of the pelvic organs and the diagnosis, pathology and treatment of practically all gynecologic conditions which are encountered. Throughout the book there is evidence of the author's vast experience as a gynecologist, endocrinologist, pathologist and teacher. The discussions are in simple language and the advice given is practical and conservative. The illustrations are abundant, beautiful and instructive. Many new ones have been added in this edition. The bibliography at the end of each chapter is limited to the best articles on the subject under discussion. The publishers should omit from their advertisement on the jacket the following sentence, "The references are chiefly to those publications most worth while, most recent and written in English." Novak properly lists many important papers which were published in the German language, and some of them were written long ago but are nevertheless of great value even today. The excellent chapter on "Common Disorders of the Female Urinary Organs" by Houston S. Everett is retained with revisions in the book. This edition, like the previous ones, should prove to be most popular and helpful to students and general practitioners because the author has produced a splendid book and the publishers also have done their part admirably.

Modern Clinical Psychiatry. By Arthur P. Noyes, M.D., Superintendent, Norristown State Hospital, Norristown, Pennsylvania. Third edition. Cloth. Price, $6. Pp. 525. W. B. Saunders Co., 218 W. Washington Sq., Philadelphia 5, 1948.

The present volume represents the third edition of Dr. Noyes' textbook of modern psychiatry. Probably the principal criticism of this work is the repeated introduction of theoretic concepts that have proved themselves inaccurate and therefore worthless. A sound school of psychiatry is the school which attempts to understand and reconstruct the dynamic mechanisms underlying personality development, both normal and abnormal. Apparently Dr. Noyes is not in complete agreement with this concept. One wishes that he had been more specific in presenting modern progress as developed during and since the last war. With the exception of the foregoing criticisms this is a good textbook. There is a reasonably good bibliography which the student is urged to use.

El electrocardiograma en la hipertensión arterial. Por Eduardo Joaquín Canabal. Tesis de doctorado. Prologado por Paul D. White. Epilogado por Riginald H. Smithwick, profesor de cirurgia, Boston University School of Medicine, Boston. Paper. Pp. 213, with 31 illustrations. El Ateneo, Florida 340, Córdoba 2099, Buenos Aires, 1947.

This thesis, appearing as a monograph, represents the work done by the author during his stay in Boston on the service of Dr. Paul D. White, who writes the foreword, and of Dr. R. H. Smithwick, who has written an addendum presenting his point of view on the value of surgery in essential hypertension. The author considers the electrocardiogram in hypertension first from the historical point of view and describes the present state of knowledge, as regards both standard and precordial leads. The electrocardiographic changes occurring postoperatively after the Smithwick operation are compared with those occurring spontaneously. An addendum is presented as to the theory of V limb leads. Much of the material in this monograph has appeared in earlier publications in English, but it is useful to have it all collected in one volume in Spanish. There are English summaries at the end of each of the seven chapters.

V 13
1948

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

BEE STING PROPHYLAXIS

To the Editor:—**A girl patient aged 5, is sensitive to bee stings. She has been stung only twice, but these were both severe episodes. She became unconscious and cyanotic within sixty seconds after the sting. The first time she was unconscious about thirty minutes; the second about two hours. She was in extreme shock. What can be done to protect this child from bee stings?** **M. A. Shillington, M.D., Glendive, Mont.**

ANSWER.—For immediate relief of this child from the symptoms of bee sting a hypodermic injection of 1:1,000 epinephrine, 0.2 cc., should be efficacious. If necessary, 0.5 cc. of epinephrine may be held under the tongue, in lieu of injection, care being taken not to swallow any of the drug. Antihistaminic drugs, such as diphenhydramine, tripelennamine or "neo-antergan" (N - [p-methoxybenzyl] - N',N' - dimethyl - N-α-pyridylethylene-diamine) may be given orally as a substitute if epinephrine is not available. In case of shock, strychnine, 1/120 to 1/100 grain (0.5 to 0.6 mg.), is the ideal relief medicament given hypodermically.

The main concern, however, is prophylaxis. This consists of hypodermic injections of aqueous or isotonic sodium chloride extracts of the ground whole body of the bee in suitable and ascending dosage. The extract can readily be prepared in any good laboratory. A proper bulk of ether-killed honey bees, e. g., 1 ounce (28 Gm.), is shaken up thoroughly with ether to remove pollen adhering to the bees' bodies, and then dried. It is then ground in a fine food grinder, and a definite weight, for instance, 5.0 Gm., is mixed with 50.0 cc. of equal parts glycerine and isotonic sodium chloride solution. After standing in the refrigerator over night the extract is filtered off through a Berkfeld or Seitz filter, to insure sterility, and labeled "bee extract 1:50 by weight-volume." Sterile glassware must of course be used throughout.

Further dilutions should be made in sterile isotonic sodium chloride solution by adding 0.5 cc. of the 1:50 extract to 9.5 cc. of sterile isotonic sodium chloride solution, giving a 1:1,000 extract by weight-volume. In the same way a 1:10,000 dilution may be prepared, by adding 1.0 cc. of the 1:1,000 extract to 9.0 cc. of isotonic sodium chloride solution. In like manner a 1:100,000 and a 1:1,000,000 dilution may be prepared.

Testing the patient may then be started by injecting 0.02 cc. of the 1:1,000,000 dilution on the flexor surface of the patient's arm intradermally. The immediate or twenty minute wheal should be noted, if any, and the twenty-four hour reaction, consisting usually of erythema. If neither of these is large enough to be significant, a similar injection may be given of 0.02 cc. of 1:100,000 dilution; and if no significant reaction is obtained, the 1:10,000 extract may be tried the next day. As soon as a significant immediate wheal or a noteworthy twenty-four hour erythema is observed, increasing doses may be given every other day until the dosage of the dilution concerned reaches 1.0 cc. A good schedule for this purpose is 0.05 cc., 0.10 cc., 0.2 cc., 0.3 cc., 0.4 cc., 0.6 cc., 0.8 cc., 1.0 cc. After that the successive higher concentrations may be employed similarly. In any case, 1.0 cc. of 1:1,000 extract should be adequate. When this dosage has been attained, it is usually advisable to discontinue treatment. Another suitable course of inoculations can be given at a later time if the patient encounters further trouble. In most cases, however, it has been found that the result is not only satisfactory from the point of view of protection, but is even permanent over a period of years.

Almost any bee keeper will be glad to furnish a small quantity of bees as an accommodation. A further precaution, however, is essential. The patient should be carefully tested for all of the prevailing pollens in his environment. Otherwise, he may be getting additional sensitization phenomena from pollen adhering abundantly to the bees' bodies and not entirely washed off by the ether. It is of course desirable, in addition, to have a general allergic testing by one familiar with allergenic technic.

PETROLEUM ASH

To the Editor:—**What is the occupational hazard involved in cleaning out boilers fired by oil, using a vacuum apparatus? My patient does this for about six months every year. His chief complaint is a bad taste in the mouth and copious expectoration. He is 40 years old and also under treatment for duodenal ulcer.**

Stephen Ivanoff, M.D., Stony Point, N. Y.

ANSWER.—The prospect of substantial damage from the residue of oil-burning furnaces is not great. In some respects such residue is similar to the fly ash from coal-burning furnaces. Fuel oils have widely scattered origins, and, correspondingly, some diversity in chemical constituency may be expected. The statements to follow definitely do not apply to all fuel oil residues. In any ash some silicates are present and at least traces of silica are expectable. Since silicates, with the exception of asbestos, are comparatively harmless, and since the content of silica is minor, no pneumonoconiosis other than benign may be anticipated even though great dustiness exists. Some fuel oils are reputed to yield an ash with a significant content of vanadium, a harmful metal. Should dust inhalation lead to vanadium poisoning, the commoner manifestations would be anemia, loss of weight, inflammation of the respiratory tract, dry cough followed by bleeding, diarrhea or constipation, renal complications and neurotic manifestations. It may be observed that these manifestations are shared by other diseases and their occurrence is not pathognomonic of vanadium poisoning. Without forecasting any probability of vanadium poisoning from the occupation mentioned, note is made of one outstanding publication on that topic: Wyers, H.: Some Toxic Effects of Vanadium Pentoxide, *British Journal of Industrial Medicine*, **3**:177, 1946. Occasionally in trades similar to the one mentioned mercury poisoning arises. The mention of marked ptyalism and foul mouth tastes suggest mercury poisoning. Among other features of that disease, the following occur: sore mouth, bleeding gums, ptyalism, discolored gums, gastroenteric ailments, foul or metallic breath, sleeplessness, melancholia, a peculiar eczema, speech difficulties, amnesia, mercurial excitement and anxiety. Since the American Standard Association's upper limit of the tolerable is only 1 mg. in the day's intake of air, any content of mercury compounds in oil ash becomes noteworthy. While mercury poisoning in the trade mentioned is certainly not common, the symptoms indicated call for further exploration.

POLAR BEAR LIVER

To the Editor:—**In several Survival Manuals published by the Armed Services it is stated that the livers of both the polar bear and the bearded seal are poisonous. I have not been able to learn what the type of poison is or whether this is an actual fact. Can you give me information or references on this subject? Is it possible that excessively high vitamin D content of the liver might cause illness?**

Charles H. Marhoefer, M.D., Randolph Field, Tex.

ANSWER.—Although it has been generally recognized that eating of polar bear liver by men and dogs usually causes severe illness, some Arctic investigators have tended to be skeptical in this regard. It has also been reported that the liver of the bearded seal is poisonous, and the opinion on this point is even less unanimous.

However, the work of K. Rodahl and T. Moore in 1939-1940, which appeared in *Biochemical Journal* (**37**:166, 1943), indicates that the toxicity is due to the high concentration of vitamin A contained in the polar bear and bearded seal liver, and the ingestion of more than small amounts of liver results in hypervitaminosis A. Reference is also made to an account by J. K. Doutt, which appeared in the *Journal of Mammalogy* (**21**:356-357, 1940).

COFFEE GROUND EMESIS

To the Editor:—**As an anesthetist I have noted on several occasions the vomiting of coffee ground fluid in the immediate postoperative period. None of the operations were related to the stomach. The cases were usually appendectomies and the pathology not that of acute appendicitis. What is the significance of such postoperative coffee ground emesis?**

Saul Dworkin, M.D., St. Louis.

ANSWER.—Duodenal ulcer, gastric ulcer or varicosities might, under certain circumstances, cause signs and symptoms leading to a diagnosis of appendicitis. Excoriations of the mucosa of the upper respiratory or digestive tract might result in swallowing of blood. Partially digested clots of blood mixed with other material in the stomach often give a characteristic "coffee ground" appearance to vomitus. There is no significance to the observations cited other than that blood or a similar substance had probably entered the stomach some time before vomiting occurred.

SUDDEN DEATH

To the Editor:—Recently a man, aged 50, died suddenly during an exciting episode while engaged in a game of cards. I had examined him about one year ago because of missed heart beats, which occurred particularly in excitement. His physical examination, including determination of blood pressure and electrocardiogram, did not reveal any abnormality. I therefore assured him that this symptom had no particular meaning, to disregard it, and prescribed a mild sedative. Since the heart standstill was caused, in all probability, by the same mechanism which caused the missed beats, could this death possibly have been prevented if I had placed this man on minimal doses of quinidine to maintain normal sinus rhythm? Might not a good many of the sudden deaths due to cardiac diseases be similar to this one, and, if so, would it not be good practice to administer quinidine in all cases of recurrent arrhythmias, as protection against such an incident? What plan and dosage should be followed?

M.D., New Jersey.

ANSWER.—Most persons who die suddenly and unexpectedly have cardiovascular disease. In a recent postmortem study of 2,030 such cases in the Borough of Manhattan, New York City, in 45 per cent death was attributed to diseases of the heart and aorta (Rabson, S. M., and Halpern, M.: Sudden and Unexpected Natural Death, Am. Heart J. **35**:635 [April] 1948).

The exact mechanism of death in the patient mentioned is of course uncertain—it may have been cardiac standstill or ventricular fibrillation. Quinidine sulfate in doses of 3 grains (0.19 Gm.) three times daily is usually effective in lessening cardiac irritability and perhaps is often life saving in preventing fatal ventricular fibrillation. For this reason protective doses are often employed during the first few weeks following myocardial infarction. Quinidine might have prevented a fatal arrhythmia in the patient cited, if such was the mechanism of his death.

No mention is made of a postmortem examination, but cardiovascular disease existed notwithstanding the normal physical examination and electrocardiogram.

PERNICIOUS ANEMIA

To the Editor:—A woman aged 38 has had pernicious anemia for the past ten years. Three months ago she noticed numbness and paresthesia of the right midthigh about the size of a saucer. She had been taking liver extract, with vitamin B capsules irregularly. She resumed the usual dosage during the latter month. The red cell count is now 3,400,000 with a color index of plus 1. The paresthesia extends from the right hip to the knee. In addition to liver extract she is receiving folic acid. Should liver extract be given by injection even if she exhibited a marked local reaction to it previously or are capsules sufficient? What is the significance of a gingivitis in this case? Is it considered contributory to the pernicious anemia or a result of it as so many dentists claim?

M.D., West Virginia.

ANSWER.—It is questionable whether the unilateral numbness in the thigh is a neural manifestation of the pernicious anemia. If there is a relationship, this symptom should improve with adequate liver therapy. Concentrated liver extract, 15 units per cubic centimeter, given parenterally every two or three weeks, is the treatment of choice in pernicious anemia.

If the local reaction occurred with an extract of hog liver, a trial should be given with beef liver extract (Lederle). Patients often lose their sensitivity to liver given parenterally if the injections are discontinued for a few months. During this time, remission may be maintained with an oral preparation of liver, 1 to 2 units daily or with 10 to 20 mg. of folic acid daily. As folic acid does not prevent the progression of cord damage, patients receiving this therapy should be observed closely for the appearance or increase of symptoms and signs referable to the nervous system.

The chronic gingivitis in this patient probably is unrelated to the pernicious anemia.

PREGNANCY TESTS

To the Editor:—What is present opinion regarding the use of rats as compared to rabbits in testing for pregnancy? What method prevails in the hospitals?

John Tennyson Myers, M.D., New York.

ANSWER.—Using rabbits in the Friedman test, with careful technic, and careful isolation of the animals to rule out false positive reactions, one may approach better than 92 per cent accuracy. By use of immature mice or rats in the Ascheim-Zondek test, the accuracy approaches 98 per cent. Usually in the latter test, more than one animal is used.

Most hospitals use the rabbits because they are possibly easier to handle; the ear vein is used for the injection.

QUINIDINE SULFATE

To the Editor:—A 63 year old patient who had severe coronary thrombosis seven years ago has been getting along fairly well since. Recently he complains of annoying extra systoles. He now takes quinidine sulfate 3 grains (0.13 Gm.) three times daily to control this symptom. Is the continued use of quinidine harmless? Is there other medication (besides barbiturates) which can be used for control of this disagreeable symptom?

M.D., New Jersey.

ANSWER.—Quinidine sulfate is the most useful drug available for control of premature beats. Rarely hypersensitivity exists; when it is present even a single dose may result in urticaria, nausea and vomiting. Most patients tolerate the drug in the dosage mentioned without difficulty for long periods of months or years without gastrointestinal or eighth nerve symptoms. The writer is acquainted with a patient who has taken quinidine sulfate in this dosage almost constantly for fifteen years. Occasionally it is mildly laxative but appears to be otherwise harmless.

Other than sedatives and the omission of caffeine and tobacco, few drugs are of special value in this connection except quinidine (or quinine). Occasionally in patients with more troublesome cardiac irritability and paroxysmal auricular tachycardia, digitalis or squill has helped when quinidine has failed.

"HAPAMINE"

To the Editor:—Are there cases on record of injections of "hapamine" causing a flare-up of rheumatoid arthritis? A 27 year old male patient without history of rheumatism was given penicillin mist and "hapamine" for sinusitis. On his fifth injection of "hapamine" pain and swelling developed in one knee. On his sixth injection, three days later, he developed hot swollen joints in one leg, high grade fever, general malaise and tenderness of sinuses. Could this be due to "hapamine?"

J. R. Busch, M.D., Laramie, Wyo.

ANSWER.—"Hapamine" is a conjugate prepared by azo linkage of histamine and despeciated horse serum globulin. Reactions to this substance are possible for several reasons. In spite of the fact that for the most part the antigenic properties of the globulin in this preparation have been modified by an enzyme process, there is an occasional evidence of a specific reaction in a horse serum sensitive person. Such a reaction would show itself by symptoms occurring within a few minutes to a few hours and consisting of one or more of the following manifestations: urticaria and angioneurotic edema, rhinitis, asthma, anaphylactic shock and other possible effects. Serum sickness type of reactions, consisting of urticarias, pains in the joints and fever, and occurring several days after the injection, are also possible. In addition, "hapamine" may act as a purely nonspecific protein and may produce such effects as described. A closer approximation could be made of the possible role of "hapamine" in the reaction under discussion if the chronologic details were given more fully. From the evidence at hand the reaction could be either coincidental or due to "hapamine." The possibility of a reaction to penicillin mist cannot be entirely ignored.

CATAPLEXY

To the Editor:—In The Journal, volume 137, page 118, May 1, 1948, appeared an inquiry concerning a "woman aged 27, who began to have periods of excessive weakness during periods of laughter." The inquirer asked about diagnosis and treatment. The answer as given is somewhat incomplete and inaccurate for the following four reasons: 1. The attacks are correctly classified as cataplexy and it is correctly stated that it is allied with catalepsy. But the most important feature of this syndrome, attacks of sleep, which gives to it the name of narcolepsy, is not mentioned. Cases of monosymptomatic cataplexy are very rare and such patients should be carefully investigated also for the presence of concomitant narcoleptic attacks. 2. The answer states that cataplexy "is an organic condition due to a structural lesion in the corpora striata." It is generally assumed, however, that the site of the lesion in narcolepsy is the hypothalamic region, and not the corpora striata. 3. Administration of "benzedrine" for the attacks of cataplexy is recommended in the answer. But "benzedrine" is beneficial in narcoleptic and has little or no influence in cataplectic attacks. Potassium chloride should be recommended for the latter, 30 to 75 grains daily by mouth (Dyson, J. B.: Cataplexy and Its Treatment, J. Nerv. & Ment. Dis. **98**:48, 1943). 4. Only 30 per cent of all cases of narcolepsy—in any form—are assumed to be postencephalitic. The statement as given in the answer that "cataplexy frequently follows an attack of epidemic encephalitis" appears doubtful therefore.

Robert Wartenberg, M.D., San Francisco.

COMMENT.—The hypothalamus is, of course, involved and so are the corpora striata. The use of potassium chloride is still in an experimental stage.—ED.